

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
28 October 2004 (28.10.2004)

PCT

(10) International Publication Number  
**WO 2004/092383 A2**

(51) International Patent Classification<sup>7</sup>: C12N 15/11

(74) Agent: GREENFIELD, Michael, S.; McDonnell  
Boehnen Hulbert and Berghoff, Suite 3100, 300 S. Wacker  
Drive, Chicago, IL 60606 (US).

(21) International Application Number:  
PCT/US2004/011320

(22) International Filing Date: 13 April 2004 (13.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/462,874	15 April 2003 (15.04.2003)	US
10/427,160	30 April 2003 (30.04.2003)	US
10/444,853	23 May 2003 (23.05.2003)	US
10/693,059	23 October 2003 (23.10.2003)	US
10/720,448	24 November 2003 (24.11.2003)	US
10/757,803	14 January 2004 (14.01.2004)	US

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): SIRNA  
THERAPEUTICS, INC. [US/US]; 2950 Wilderness  
Place, Boulder, CO 80301 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): MCSWIGGEN,  
James [US/US]; 4866 Franklin Dr., Boulder, CO 80301  
(US). BHARAT, Chowira [US/US]; 576 Manorwood  
Lane, Louisville, CO 80027 (US). HAEBERLI, Peter  
[US/US]; 705 7th Street, Berthoud, CO 80513 (US).

Published:

— without international search report and to be republished  
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE RESPIRATORY SYNDROME (SARS) VIRUS GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siNA)

(57) Abstract: The present invention comprises compounds, compositions, and methods useful for modulating the expression of genes associated with respiratory and pulmonary disease, such as severe acute respiratory syndrome (SARS) virus genes, using short interfering nucleic acid (siNA) molecules. This invention also comprises compounds, compositions, and methods useful for modulating the expression and activity of SARS virus genes, or other genes involved in pathways of SARS virus gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of SARS virus RNA.



WO 2004/092383 A2

**RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE  
RESPIRATORY SYNDROME (SARS) VIRUS GENE EXPRESSION USING  
SHORT INTERFERING NUCLEIC ACID (siNA)**

This application claims the benefit of U.S. Provisional Application No. 5 60/462,874, filed April 15, 2003, and is a continuation-in-part of U.S. Patent Application No. 10/757,803, filed January 14, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/720,448, filed November 24, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/693,059, filed October 23, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/444,853, filed May 23, 2003. This application 10 is also a continuation-in-part of US Patent Application No. 10/427,160, filed April 30, 2003.

Reference is made to International Patent Application No. PCT/US03/05346, filed February 20, 2003, and International Patent Application No. PCT/US03/05028, filed February 20, 2003, both of which claim the benefit of U.S. Provisional Application No. 15 60/358,580 filed February 20, 2002, U.S. Provisional Application No. 60/363,124 filed March 11, 2002, U.S. Provisional Application No. 60/386,782 filed June 6, 2002, U.S. Provisional Application No. 60/406,784 filed August 29, 2002, U.S. Provisional Application No. 60/408,378 filed September 5, 2002, U.S. Provisional Application No. 60/409,293 filed September 9, 2002, and U.S. Provisional Application No. 60/440,129 20 filed January 15, 2003. Reference is also made to International Patent Application No. PCT/US02/15876 filed May 17, 2002.

All the listed applications are hereby incorporated by reference herein in their entireties, including the drawings.

**Field Of The Invention**

25       The present invention concerns compounds, compositions, and methods for the study, diagnosis, and treatment of diseases and conditions that respond to the modulation of severe acute respiratory syndrome (SARS) associated coronavirus (SARS virus) gene expression and/or activity. The present invention also concerns compounds, compositions, and methods relating to conditions and diseases that respond to the 30 modulation of expression and/or activity of genes involved in SARS virus pathways of

gene expression, including cellular genes that are involved in SARS virus infection. Specifically, the invention comprises small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules capable of  
5 mediating RNA interference (RNAi) against severe acute respiratory syndrome (SARS) associated coronavirus gene expression.

### Background Of The Invention

The following is a discussion of relevant art pertaining to RNAi. The discussion is provided only for understanding of the invention that follows. The summary is not an  
10 admission that any of the work described below is prior art to the claimed invention.

RNA interference refers to the process of sequence-specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Fire *et al.*, 1998, *Nature*, 391, 806; Hamilton *et al.*, 1999, *Science*, 286, 950-951; Lin *et al.*, 1999, *Nature*, 402, 128-129; Sharp, 1999, *Genes &*  
15 *Dev.*, 13:139-141; and Strauss, 1999, *Science*, 286, 886). The corresponding process in plants (Heifetz *et al.*, International PCT Publication No. WO 99/61631) is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression  
20 of foreign genes and is commonly shared by diverse flora and phyla (Fire *et al.*, 1999, *Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or from the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or  
25 viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response through a mechanism that has yet to be fully characterized. This mechanism appears to be different from other known mechanisms involving double stranded RNA-specific ribonucleases, such as the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2',5'-oligoadenylate synthetase resulting in non-  
30 specific cleavage of mRNA by ribonuclease L (see for example US Patent Nos.

6,107,094; 5,898,031; Clemens *et al.*, 1997, *J. Interferon & Cytokine Res.*, 17, 503-524; Adah *et al.*, 2001, *Curr. Med. Chem.*, 8, 1189).

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as dicer (Bass, 2000, *Cell*, 101, 235; Zamore *et al.*, 2000, *Cell*, 101, 25-33; Hammond *et al.*, 2000, *Nature*, 404, 293). Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Bass, 2000, *Cell*, 101, 235; Bernstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). Dicer has also been implicated in the excision of 21 and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence complementary to the antisense strand of the siRNA duplex. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188).

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Bahramian and Zarbl, 1999, *Molecular and Cellular Biology*, 19, 274-283 and Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mammalian systems. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.*, 2001, *Nature*, 411, 494 and Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in *Drosophila* embryonic lysates (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164) has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21-nucleotide siRNA duplexes are most active when containing 3'-terminal dinucleotide



overhangs. Furthermore, complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of the 3'-terminal siRNA overhang nucleotides with 2'-deoxy nucleotides (2'-H) was shown to be tolerated. Single mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end of the guide sequence (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.*, 2001, *Cell*, 107, 309).

Studies have shown that replacing the 3'-terminal nucleotide overhanging segments of a 21-mer siRNA duplex having two-nucleotide 3'-overhangs with deoxyribonucleotides does not have an adverse effect on RNAi activity. Replacing up to four nucleotides on each end of the siRNA with deoxyribonucleotides has been reported to be well tolerated, whereas complete substitution with deoxyribonucleotides results in no RNAi activity (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164). In addition, Elbashir *et al.*, *supra*, also report that substitution of siRNA with 2'-O-methyl nucleotides completely abolishes RNAi activity. Li *et al.*, International PCT Publication No. WO 00/44914, and Beach *et al.*, International PCT Publication No. WO 01/68836 preliminarily suggest that siRNA may include modifications to either the phosphate-sugar backbone or the nucleoside to include at least one of a nitrogen or sulfur heteroatom, however, neither application postulates to what extent such modifications would be tolerated in siRNA molecules, nor provides any further guidance or examples of such modified siRNA. Kreutzer *et al.*, Canadian Patent Application No. 2,359,180, also describe certain chemical modifications for use in dsRNA constructs in order to counteract activation of double-stranded RNA-dependent protein kinase PKR, specifically 2'-amino or 2'-O-methyl nucleotides, and nucleotides containing a 2'-O or 4'-C methylene bridge. However, Kreutzer *et al.* similarly fails to provide examples or guidance as to what extent these modifications would be tolerated in dsRNA molecules.

Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, tested certain chemical modifications targeting the *unc-22* gene in *C. elegans* using long (>25 nt) siRNA transcripts. The authors describe the introduction of thiophosphate residues into these siRNA transcripts by incorporating thiophosphate nucleotide analogs with T7 and T3  
5 RNA polymerase and observed that RNAs with two phosphorothioate modified bases also had substantial decreases in effectiveness as RNAi. Further, Parrish *et al.* reported that phosphorothioate modification of more than two residues greatly destabilized the RNAs *in vitro* such that interference activities could not be assayed. *Id.* at 1081. The authors also tested certain modifications at the 2'-position of the nucleotide sugar in the  
10 long siRNA transcripts and found that substituting deoxynucleotides for ribonucleotides produced a substantial decrease in interference activity, especially in the case of Uridine to Thymidine and/or Cytidine to deoxy-Cytidine substitutions. *Id.* In addition, the authors tested certain base modifications, including substituting, in sense and antisense strands of the siRNA, 4-thiouracil, 5-bromouracil, 5-iodouracil, and 3-(aminoallyl)uracil  
15 for uracil, and inosine for guanosine. Whereas 4-thiouracil and 5-bromouracil substitution appeared to be tolerated, Parrish reported that inosine produced a substantial decrease in interference activity when incorporated in either strand. Parrish also reported that incorporation of 5-iodouracil and 3-(aminoallyl)uracil in the antisense strand resulted in a substantial decrease in RNAi activity as well.

20 The use of longer dsRNA has been described. For example, Beach *et al.*, International PCT Publication No. WO 01/68836, describes specific methods for attenuating gene expression using endogenously-derived dsRNA. Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe a *Drosophila in vitro* RNAi system and the use of specific siRNA molecules for certain functional genomic and  
25 certain therapeutic applications; although Tuschl, 2001, *Chem. Biochem.*, 2, 239-245, doubts that RNAi can be used to cure genetic diseases or viral infection due to the danger of activating interferon response. Li *et al.*, International PCT Publication No. WO 00/44914, describe the use of specific long (141 bp-488 bp) enzymatically synthesized or vector expressed dsRNAs for attenuating the expression of certain target genes.  
30 Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646, describe certain methods for inhibiting the expression of particular genes in mammalian cells using certain long (550 bp-714 bp), enzymatically synthesized or vector expressed dsRNA

molecules. Fire *et al.*, International PCT Publication No. WO 99/32619, describe particular methods for introducing certain long dsRNA molecules into cells for use in inhibiting gene expression in nematodes. Plactinck *et al.*, International PCT Publication No. WO 00/01846, describe certain methods for identifying specific genes responsible for conferring a particular phenotype in a cell using specific long dsRNA molecules. Mello *et al.*, International PCT Publication No. WO 01/29058, describe the identification of specific genes involved in dsRNA-mediated RNAi. Pachuck *et al.*, International PCT Publication No. WO 00/63364, describe certain long (at least 200 nucleotide) dsRNA constructs. Deschamps Depaillette *et al.*, International PCT Publication No. WO 99/07409, describe specific compositions consisting of particular dsRNA molecules combined with certain anti-viral agents. Waterhouse *et al.*, International PCT Publication No. 99/53050 and 1998, *PNAS*, 95, 13959-13964, describe certain methods for decreasing the phenotypic expression of a nucleic acid in plant cells using certain dsRNAs. Driscoll *et al.*, International PCT Publication No. WO 01/49844, describe specific DNA expression constructs for use in facilitating gene silencing in targeted organisms.

Others have reported on various RNAi and gene-silencing systems. For example, Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, describe specific chemically-modified dsRNA constructs targeting the unc-22 gene of *C. elegans*. Grossniklaus, International PCT Publication No. WO 01/38551, describes certain methods for regulating polycomb gene expression in plants using certain dsRNAs. Churikov *et al.*, International PCT Publication No. WO 01/42443, describe certain methods for modifying genetic characteristics of an organism using certain dsRNAs. Cogoni *et al.*, International PCT Publication No. WO 01/53475, describe certain methods for isolating a *Neurospora* silencing gene and uses thereof. Reed *et al.*, International PCT Publication No. WO 01/68836, describe certain methods for gene silencing in plants. Honer *et al.*, International PCT Publication No. WO 01/70944, describe certain methods of drug screening using transgenic nematodes as Parkinson's Disease models using certain dsRNAs. Deak *et al.*, International PCT Publication No. WO 01/72774, describe certain *Drosophila*-derived gene products that may be related to RNAi in *Drosophila*. Arndt *et al.*, International PCT Publication No. WO 01/92513 describe certain methods for mediating gene suppression by using factors that enhance RNAi. Tuschl *et al.*,

International PCT Publication No. WO 02/44321, describe certain synthetic siRNA constructs. Pachuk *et al.*, International PCT Publication No. WO 00/63364, and Satishchandran *et al.*, International PCT Publication No. WO 01/04313, describe certain methods and compositions for inhibiting the function of certain polynucleotide sequences using certain long (over 250 bp), vector expressed dsRNAs. Echeverri *et al.*, International PCT Publication No. WO 02/38805, describe certain *C. elegans* genes identified via RNAi. Kreutzer *et al.* International PCT Publications Nos. WO 02/055692, WO 02/055693, and EP 1144623 B1 describes certain methods for inhibiting gene expression using dsRNA. Graham *et al.*, International PCT Publications Nos. WO 99/49029 and WO 01/70949, and AU 4037501 describe certain vector expressed siRNA molecules. Fire *et al.*, US 6,506,559, describe certain methods for inhibiting gene expression in vitro using certain long dsRNA (299 bp-1033 bp) constructs that mediate RNAi. Martinez *et al.*, 2002, *Cell*, 110, 563-574, describe certain single stranded siRNA constructs, including certain 5'-phosphorylated single stranded siRNAs that mediate RNA interference in Hela cells. Harborth *et al.*, 2003, *Antisense & Nucleic Acid Drug Development*, 13, 83-105, describe certain chemically and structurally modified siRNA molecules. Chiu and Rana, 2003, *RNA*, 9, 1034-1048, describe certain chemically and structurally modified siRNA molecules.

McCaffrey *et al.*, 2002, *Nature*, 418, 38-39, describes the use of certain siRNA constructs targeting a chimeric SARS NS5B protein/luciferase transcript in mice.

Randall *et al.*, 2003, *PNAS USA*, 100, 235-240, describe certain siRNA constructs targeting SARS RNA in Huh7 hepatoma cell lines.

## SUMMARY OF THE INVENTION

This invention comprises compounds, compositions, and methods useful for modulating the expression of genes associated with the development or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and/or other disease states associated with SARS virus infection, using short interfering nucleic acid (siNA) molecules. This invention also comprises compounds, compositions, and methods useful

for modulating the expression and activity of severe acute respiratory syndrome (SARS) associated coronavirus or genes involved in severe acute respiratory syndrome (SARS) associated coronavirus gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of severe acute respiratory syndrome (SARS) associated coronavirus. For convenience, all forms of the small nucleic acid molecules of the invention (*e.g.*, siRNA, dsRNA, micro-RNA, etc.) are referred to herein as "siNA," unless expressly stated otherwise.

A siNA of the invention can be unmodified or chemically-modified. A siNA of the instant invention can be chemically synthesized, expressed from a vector or enzymatically synthesized. The instant invention also features various chemically-modified synthetic short interfering nucleic acid (siNA) molecules capable of modulating repeat expansion gene expression or activity in cells by RNA interference (RNAi). The use of chemically-modified siNA improves various properties of native siNA molecules through increased resistance to nuclease degradation *in vivo* and/or through improved cellular uptake. Further, contrary to earlier published studies, siNA having multiple chemical modifications retains its RNAi activity. The siNA molecules of the instant invention are useful reagents and are useful in methods for a variety of therapeutic, diagnostic, target validation, genomic discovery, genetic engineering, and pharmacogenomic applications.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of gene(s) encoding SARS virus. Specifically, the present invention comprises siNA molecules that modulate the expression of SARS proteins, for example, proteins encoded by SARS virus genome, such as Genbank Accession Nos. in Table I.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of genes representing cellular targets for SARS virus infection, such as cellular receptors,

cell surface molecules, cellular enzymes, cellular transcription factors, and/or cytokines, second messengers, and cellular accessory molecules.

Due to the high sequence variability of the SARS genome, selection of siNA molecules for broad therapeutic applications preferably involve the conserved regions of the SARS genome. In one embodiment, the present invention comprises siNA molecules that target the conserved regions of the SARS genome, such as the polymerase encoding region of the SARS virus genomic RNA. Therefore, siNA molecules of the invention are designed to target all the different isolates of SARS. siNA molecules designed to target conserved regions of various SARS isolates enable efficient inhibition of SARS replication in diverse patient populations and ensure the effectiveness of the siNA molecules against SARS quasi species that evolve due to mutations in the non-conserved regions of the SARS genome. Therefore, a single siNA molecule can be targeted against all isolates of SARS by designing the siNA molecule to interact with conserved nucleotide sequences of SARS (such conserved sequences are expected to be present in the RNA of all SARS isolates).

In one embodiment, a siNA molecule is designed to target the 3'-untranslated region and/or the shared leader sequence of genomic SARS RNA transcripts. Because SARS coronavirus mRNAs are nested with the genomic RNA and share common 3' region and polyA region, a single siNA targeting the 3'-end can target all transcripts plus the genomic RNA.

In one embodiment, a siNA molecule of the invention targets both the plus (genomic) strand RNA and minus strand RNA of the SARS virus. Because the SARS virus generates a minus strand RNA from plus strand genomic RNA, a double stranded siNA molecule targeting the plus strand will also target the minus strand, thus allowing a single double-stranded siNA to target both the plus (genomic) and the minus strand of the SARS virus. For example, a double stranded siNA molecule targeting the 3'-end of the SARS virus genomic strand will also target the 3'-end of the the minus strand, thus allowing a single double-stranded siNA to target both the plus and the minus strand of the SARS virus.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of gene(s) encoding SARS virus and/or cellular proteins associated with the maintenance or development of SARS virus infection and/or acute respiratory failure, viral pneumonia, such as genes encoding sequences comprising those sequences referred to by GenBank Accession Nos. shown in Table I, referred to herein generally as SARS. The description below of the various aspects and embodiments of the invention is provided with reference to exemplary severe acute respiratory syndrome (SARS) associated coronavirus genes, generally referred to herein as SARS. However, such reference is meant to be exemplary only and the various aspects and embodiments of the invention are also directed to other genes that express alternate SARS genes, such as mutant SARS genes, splice variants of SARS genes, and genes encoding different strains of SARS, as well as as cellular targets for SARS, such as those described herein. The various aspects and embodiments are also directed to other genes involved in SARS pathways, including genes that encode cellular proteins involved in the maintenance and/or development of SARS virus infection and/or acute respiratory failure or other genes that express other proteins associated with SARS virus infection, such as cellular proteins that are utilized in the SARS life-cycle. Such additional genes can be analyzed for target sites using the methods described herein for SARS. Thus, the inhibition and the effects of such inhibition of the other genes can be performed as described herein. In other words, the term "SARS" as it is defined herein below and recited in the described embodiments, is meant to encompass genes associated with the development or maintenance of SARS virus infection, such as genes which encode SARS polypeptides, including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as well as cellular genes involved in SARS pathways of gene expression, replication, and/or SARS activity. Also, the term "SARS" as it is defined herein and recited in the described embodiments, is meant to encompass SARS viral gene products and cellular gene products involved in SARS virus infection, such as those described herein. Thus, each of the embodiments described herein with reference to the term "SARS" are applicable to all of the virus, cellular and viral protein, peptide, polypeptide, and/or polynucleotide molecules covered by the term "SARS" as that term is defined herein.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a severe acute respiratory syndrome virus (e.g., SARS) gene, wherein said siNA molecule comprises about 19 to about 23 base pairs. Preferably the number of based pairs in the siNA molecule is 18, 19, 20, 21, 22, 23, or 24.

In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene comprises SARS encoding sequence. In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene comprises SARS non-coding sequence or regulatory elements involved in SARS gene expression.

In one embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to any RNA having SARS encoding sequence, such as those sequences having GenBank Accession Nos. shown in Table I. In another embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to an RNA having other SARS encoding sequence, for example other mutant SARS genes not shown in Table I but known in the art to be associated with respiratory and/or pulmonary disease, SARS virus infection and/or acute respiratory failure, viral pneumonia, impeded respiration, respiratory distress syndrome, pulmonary hypertension, or pulmonary vasoconstriction. Chemical modifications as shown in Tables III and IV or otherwise described herein can be applied to any siNA construct of the invention. In another embodiment, a siNA molecule of the invention includes nucleotide sequence that can interact with nucleotide sequence of a SARS gene and thereby mediate silencing of SARS gene expression, for example, wherein the siNA mediates regulation of SARS gene expression by cellular processes that modulate the chromatin structure of the SARS gene and prevent transcription of the SARS gene.

In another embodiment, the invention features a siNA molecule comprising nucleotide sequence, for example, nucleotide sequence in the antisense region of the siNA molecule that is complementary to a nucleotide sequence or portion of sequence of



a SARS gene. In another embodiment, the invention features a siNA molecule comprising a region, for example, the antisense region of the siNA construct, complementary to a sequence comprising a SARS gene sequence or a portion thereof.

In one embodiment, the antisense region of SARS siNA constructs can comprise a sequence complementary to sequence having any of SEQ ID NOs. 1-1651 or 3303-3318. In one embodiment, the antisense region can also comprise sequence having any of SEQ ID NOs. 1652-3302, 3319-3326, 3335-3342, 3351-3358, 3367-3374, 3376, 3378, 3380, 3383, 3385, 3387, 3389, or 3392. In another embodiment, the sense region of the SARS constructs can comprise sequence having any of SEQ ID NOs. 1-1651, 3303-3310, 3311-3318, 3327-3334, 3343-3350, 3359-3366, 3375, 3377, 3379, 3381, 3382, 3384, 3386, 3388, 3390, or 3391.

In one embodiment, a siNA molecule of the invention comprises any of SEQ ID NOs. 1-3392. The sequences shown in SEQ ID NOs: 1-3392 are not limiting. A siNA molecule of the invention can comprise any contiguous SARS sequence (e.g., about 19 to about 25, or about 19, 20, 21, 22, 23, 24 or 25 contiguous SARS nucleotides).

In yet another embodiment, the invention features a siNA molecule comprising a sequence, for example, the antisense sequence of the siNA construct, complementary to a sequence or portion of sequence comprising sequence represented by GenBank Accession Nos. shown in Table I. Chemical modifications in Tables III and IV and described herein can be applied to any siNA construct of the invention. siNA molecules of the invention are unmodified or have up to all nucleotides modified with modifications according to Tables III and IV.

In one embodiment of the invention a siNA molecule comprises an antisense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense strand is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a sense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, and wherein said sense strand and said antisense strand are distinct nucleotide sequences with at least about 19 complementary nucleotides.

In another embodiment of the invention a siNA molecule of the invention comprises an antisense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense region is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a sense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein said sense region and said antisense region comprise a linear molecule with at least about 19 complementary nucleotides.

In one embodiment of the invention a siNA molecule comprises an antisense strand comprising a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof encoding a SARS protein. The siNA further comprises a sense strand, wherein said sense strand comprises a nucleotide sequence of a SARS gene or a portion thereof.

In another embodiment, a siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence encoding a SARS protein or a portion thereof. The siNA molecule further comprises a sense region, wherein said sense region comprises a nucleotide sequence of a SARS gene or a portion thereof.

In one embodiment, a siNA molecule of the invention has RNAi activity that modulates expression of RNA encoded by a SARS gene. Because SARS genes can share some degree of sequence homology with each other, siNA molecules can be designed to target a class of SARS genes or alternately specific SARS genes by selecting sequences that are either shared among different SARS targets (e.g., different viral strains) or alternatively that are unique for a specific SARS target (e.g., a particular viral strain). Therefore, in one embodiment, the siNA molecule can be designed to target conserved regions of SARS RNA sequences having homology among several SARS genes so as to target several SARS genes (e.g., different SARS isoforms, splice variants, mutant genes etc.) with one siNA molecule. In another embodiment, the siNA molecule can be designed to target a sequence that is unique to a specific SARS RNA sequence due to the high degree of specificity that the siNA molecule requires to mediate RNAi activity.

In one embodiment, nucleic acid molecules of the invention that act as mediators of the RNA interference gene silencing response are double-stranded nucleic acid molecules. In another embodiment, the siNA molecules of the invention consist of duplexes containing about 19 base pairs between oligonucleotides comprising about 19 to about 25 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, or 26) nucleotides. In yet another embodiment, siNA molecules of the invention comprise duplexes with overhanging ends of about about 1 to about 3 (e.g., 1, 2, 3, or 4) nucleotides, for example, about 21-nucleotide duplexes with about 19 base pairs and 3'-terminal mononucleotide, dinucleotide, or trinucleotide overhangs.

In one embodiment, the invention features one or more chemically-modified siNA constructs having specificity for SARS expressing nucleic acid molecules, such as RNA encoding a SARS protein. Non-limiting examples of such chemical modifications include without limitation phosphorothioate internucleotide linkages, 2'-deoxyribonucleotides, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides, "universal base" nucleotides, "acyclic" nucleotides, 5-C-methyl nucleotides, and terminal glyceryl and/or inverted deoxy abasic residue incorporation. These chemical modifications, when used in various siNA constructs, are shown to preserve RNAi activity in cells while at the same time, dramatically increasing the serum stability of these compounds. Furthermore, contrary to the data published by Parrish *et al.*, *supra*, applicant demonstrates that multiple (greater than one) phosphorothioate substitutions are well-tolerated and confer substantial increases in serum stability for modified siNA constructs.

In one embodiment, a siNA molecule of the invention comprises modified nucleotides while maintaining the ability to mediate RNAi. The modified nucleotides can be used to improve *in vitro* or *in vivo* characteristics such as stability, activity, and/or bioavailability. For example, a siNA molecule of the invention can comprise modified nucleotides as a percentage of the total number of nucleotides present in the siNA molecule. As such, a siNA molecule of the invention can generally comprise about 5% to about 100% modified nucleotides (e.g., 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% modified nucleotides). The actual percentage of modified nucleotides present in a given siNA

molecule will depend on the total number of nucleotides present in the siNA. If the siNA molecule is single stranded, the percent modification can be based upon the total number of nucleotides present in the single stranded siNA molecules. Likewise, if the siNA molecule is double stranded, the percent modification can be based upon the total  
5 number of nucleotides present in the sense strand, antisense strand, or both the sense and antisense strands.

One aspect of the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene. In one embodiment, a double stranded siNA molecule comprises one or more chemical  
10 modifications and each strand of the double-stranded siNA is about 21 nucleotides long. In one embodiment, the double-stranded siNA molecule does not contain any ribonucleotides. In another embodiment, the double-stranded siNA molecule comprises one or more ribonucleotides. In one embodiment, each strand of the double-stranded siNA molecule comprises about 19 to about 23 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26,  
15 27, 28, or 29) nucleotides, wherein each strand comprises about 19 nucleotides that are complementary to the nucleotides of the other strand. In one embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof of the SARS gene, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence  
20 substantially similar to the nucleotide sequence of the SARS gene or a portion thereof.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of the SARS gene or a portion  
25 thereof, and a sense region, wherein the sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In one embodiment, the antisense region and the sense region each comprise about 19 to about 23 (e.g. about 19, 20, 21, 22, or 23) nucleotides, wherein the antisense region comprises about 19 nucleotides that are complementary to nucleotides of the sense  
30 region.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA  
5 encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region.

In one embodiment, the SARS virus RNA contemplated by the invention comprises SARS virus minus strand RNA. In another embodiment, the SARS virus RNA contemplated by the invention comprises SARS virus plus strand RNA.

10 In one embodiment, a siNA molecule of the invention comprises blunt ends, i.e., ends that do not include any overhanging nucleotides. For example, a siNA molecule of the invention comprising modifications described herein (e.g., comprising nucleotides having Formulae I-VII or siNA constructs comprising Stab00-Stab22 or any combination thereof (see Table IV)) and/or any length described herein can comprise blunt ends or  
15 ends with no overhanging nucleotides.

In one embodiment, any siNA molecule of the invention can comprise one or more blunt ends, i.e., where a blunt end does not have any overhanging nucleotides. In a non-limiting example, a blunt ended siNA molecule has a number of base pairs equal to the number of nucleotides present in each strand of the siNA molecule. In another example,  
20 a siNA molecule comprises one blunt end, for example wherein the 5'-end of the antisense strand and the 3'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises one blunt end, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises two blunt  
25 ends, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand as well as the 5'-end of the antisense strand and 3'-end of the sense strand do not have any overhanging nucleotides. A blunt ended siNA molecule can comprise, for example, from about 18 to about 30 nucleotides (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides). Other nucleotides present in a blunt ended siNA  
30 molecule can comprise mismatches, bulges, loops, or wobble base pairs, for example, to modulate the activity of the siNA molecule to mediate RNA interference.

By "blunt ends" is meant symmetric termini or termini of a double stranded siNA molecule having no overhanging nucleotides. The two strands of a double stranded siNA molecule align with each other without over-hanging nucleotides at the termini. For example, a blunt ended siNA construct comprises terminal nucleotides that are  
5 complementary between the sense and antisense regions of the siNA molecule.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the  
10 antisense region of the siNA molecule. The sense region can be connected to the antisense region via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker.

In one embodiment, the invention features double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein  
15 the siNA molecule comprises about 19 to about 21 base pairs, and wherein each strand of the siNA molecule comprises one or more chemical modifications. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a  
20 nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the  
25 nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises no ribonucleotides. In another embodiment, a siNA molecule of the invention comprises ribonucleotides.

5 In one embodiment, a siNA molecule of the invention comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the siNA further comprises a sense region comprising a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In another embodiment, the antisense region and the sense region each comprise about 19 to about 23 nucleotides and the antisense region  
10 comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS gene, or a  
15 portion thereof, and the sense region comprises a nucleotide sequence that is complementary to the antisense region. In another embodiment, the siNA molecule is assembled from two separate oligonucleotide fragments, wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment, the sense region is connected to the  
20 antisense region via a linker molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule, such as a nucleotide or non-nucleotide linker. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, the invention features a double-stranded short interfering  
25 nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region, and wherein the siNA  
30 molecule has one or more modified pyrimidine and/or purine nucleotides. In one embodiment, the pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine

nucleotides or 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides.

5 In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In one embodiment, the pyrimidine nucleotides in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the antisense region are 2'-O-methyl or 2'-deoxy purine nucleotides. In

10 another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the sense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein

15 the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule, and wherein the fragment comprising the sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment. In another embodiment, the terminal cap moiety is an inverted

20 deoxy abasic moiety or glyceryl moiety. In another embodiment, each of the two fragments of the siNA molecule comprise about 21 nucleotides.

In one embodiment, the invention features a siNA molecule comprising at least one modified nucleotide, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. The siNA can be, for example, of length between about 12 and about 36 nucleotides. In

25 another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another

30 embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-



deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a method of increasing the stability of a siNA molecule against cleavage by ribonucleases comprising introducing at least one modified nucleotide into the siNA molecule, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. In another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a

nucleotide sequence that is complementary to the antisense region, and wherein the purine nucleotides present in the antisense region comprise 2'-deoxy- purine nucleotides. In an alternative embodiment, the purine nucleotides present in the antisense region comprise 2'-O-methyl purine nucleotides. In either of the above embodiments, the antisense region can comprise a phosphorothioate internucleotide linkage at the 3' end of the antisense region. Alternatively, in either of the above embodiments, the antisense region can comprise a glyceryl modification at the 3' end of the antisense region. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the antisense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the antisense region of a siNA molecule of the invention comprises sequence complementary to a portion of a SARS transcript having sequence unique to a particular SARS disease related allele, such as sequence comprising a SNP associated with the disease specific allele. As such, the antisense region of a siNA molecule of the invention can comprise sequence complementary to sequences that are unique to a particular allele to provide specificity in mediating selective RNAi against the disease related allele.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule. In one embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine nucleotide, such as a 2'-deoxy-thymidine. In another embodiment, all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the

RNA encoded by the SARS gene. In another embodiment, about 21 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the SARS gene. In any of the above embodiments, the 5'-end of the fragment comprising said antisense region can optionally includes a phosphate group.

- 5        In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits the expression of a SARS RNA sequence (e.g., wherein said target RNA sequence is encoded by a SARS gene involved in the SARS pathway), wherein the siNA molecule does not contain any ribonucleotides and wherein each strand of the double-stranded siNA molecule is about 21 nucleotides long.
- 10       Examples of non-ribonucleotide containing siNA constructs are combinations of stabilization chemistries shown in Table IV in any combination of Sense/Antisense chemistries, such as Stab 7/8, Stab 7/11, Stab 8/8, Stab 18/8, Stab 18/11, Stab 12/13, Stab 7/13, Stab 18/13, Stab 7/19, Stab 8/19, Stab 18/19, Stab 7/20, Stab 8/20, or Stab 18/20.
- 15       In one embodiment, the invention features a chemically synthesized double stranded RNA molecule that directs cleavage of a SARS RNA via RNA interference, wherein each strand of said RNA molecule is about 21 to about 23 nucleotides in length; one strand of the RNA molecule comprises nucleotide sequence having sufficient complementarity to the SARS RNA for the RNA molecule to direct cleavage of the
- 20       SARS RNA via RNA interference; and wherein at least one strand of the RNA molecule comprises one or more chemically modified nucleotides described herein, such as deoxynucleotides, 2'-O-methyl nucleotides, 2'-deoxy-2'-fluoro nucleotides, 2'-O-methoxyethyl nucleotides etc.

- 25       In one embodiment, the invention features a medicament comprising a siNA molecule of the invention.

In one embodiment, the invention features an active ingredient comprising a siNA molecule of the invention.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule to down-regulate expression of a SARS gene,

wherein the siNA molecule comprises one or more chemical modifications and each strand of the double-stranded siNA is about 18 to about 28 or more (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or more) nucleotides long.

5 In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense  
10 strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises  
15 nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

20 In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA that encodes a protein or portion thereof, the other strand is a sense strand which comprises  
25 nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded  
30 siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other

strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, each strand of the siNA molecule comprises about 18 to about 29 or more (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein each strand comprises at least about 18 nucleotides that are complementary to the nucleotides of the other strand. In another embodiment, the siNA molecule is assembled from two oligonucleotide fragments, wherein one fragment comprises the nucleotide sequence of the antisense strand of the siNA molecule and a second fragment comprises nucleotide sequence of the sense region of the siNA molecule. In yet another embodiment, the sense strand is connected to the antisense strand via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker. In a further embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In still another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides. In another embodiment, the antisense strand comprises one or more 2'-deoxy-2'-fluoro pyrimidine nucleotides and one or more 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-O-methyl purine nucleotides. In a further embodiment the sense strand comprises a 3'-end and a 5'-end, wherein a terminal cap moiety (e.g., an inverted deoxy abasic moiety or inverted deoxy nucleotide moiety such as inverted thymidine) is present at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand. In another embodiment, the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense strand. In another embodiment, the antisense strand comprises a glyceryl modification at the 3' end. In another embodiment, the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein each of the two strands of the siNA molecule comprises about 21 nucleotides. In one embodiment, about 21 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule, wherein at least two 3' terminal nucleotides of each strand of the siNA molecule are not base-paired to the nucleotides of the other strand of the siNA molecule. In another embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine, such as 2'-deoxy-thymidine. In another embodiment, each strand of the siNA molecule is base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof. In another embodiment, about 21 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence or a portion thereof of the antisense strand is complementary to a nucleotide sequence of the untranslated region or a portion thereof of the SARS RNA.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand, wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence of the antisense strand is complementary to a nucleotide sequence of the SARS RNA or a portion thereof that is present in the SARS RNA.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention in a pharmaceutically acceptable carrier or diluent.

In a non-limiting example, the introduction of chemically-modified nucleotides into nucleic acid molecules provides a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to native RNA molecules that are delivered exogenously. For example, the use of chemically-modified nucleic acid molecules can enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect since chemically-modified nucleic acid molecules tend to have a longer half-life in serum. Furthermore, certain chemical modifications can improve the bioavailability of nucleic acid molecules by targeting particular cells or tissues and/or improving cellular uptake of the nucleic acid molecule. Therefore, even if the activity of

a chemically-modified nucleic acid molecule is reduced as compared to a native nucleic acid molecule, for example, when compared to an all-RNA nucleic acid molecule, the overall activity of the modified nucleic acid molecule can be greater than that of the native molecule due to improved stability and/or delivery of the molecule. Unlike native  
5 unmodified siNA, chemically-modified siNA can also minimize the possibility of activating interferon activity in humans.

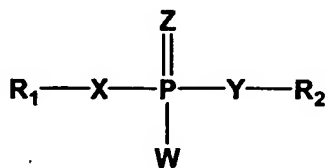
In any of the embodiments of siNA molecules described herein, the antisense region of a siNA molecule of the invention can comprise a phosphorothioate internucleotide linkage at the 3'-end of said antisense region. In any of the embodiments  
10 of siNA molecules described herein, the antisense region can comprise about one to about five phosphorothioate internucleotide linkages at the 5'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs of a siNA molecule of the invention can comprise ribonucleotides or deoxyribonucleotides that are chemically-modified at a nucleic acid sugar, base, or  
15 backbone. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more universal base ribonucleotides. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more acyclic nucleotides.

One embodiment of the invention provides an expression vector comprising a  
20 nucleic acid sequence encoding at least one siNA molecule of the invention in a manner that allows expression of the nucleic acid molecule. Another embodiment of the invention provides a mammalian cell comprising such an expression vector. The mammalian cell can be a human cell. The siNA molecule of the expression vector can comprise a sense region and an antisense region. The antisense region can comprise  
25 sequence complementary to a RNA or DNA sequence encoding SARS and the sense region can comprise sequence complementary to the antisense region. The siNA molecule can comprise two distinct strands having complementary sense and antisense regions. The siNA molecule can comprise a single strand having complementary sense and antisense regions.



In one embodiment, the nucleotide sequence of the antisense strand or a portion thereof of a siNA molecule of the invention is complementary to the nucleotide sequence of a SARS RNA or a portion thereof that is present in the RNA of all SARS isolates.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides comprising a backbone modified internucleotide linkage having Formula I:

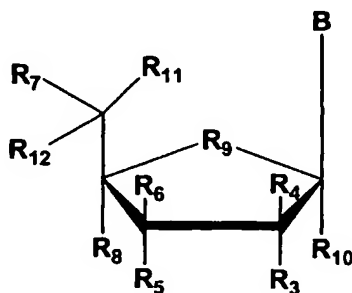


wherein each R1 and R2 is independently any nucleotide, non-nucleotide, or polynucleotide which can be naturally-occurring or chemically-modified, each X and Y is independently O, S, N, alkyl, or substituted alkyl, each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, or acetyl and wherein W, X, Y, and Z are optionally not all O. In another embodiment, a backbone modification of the invention comprises a phosphonoacetate and/or thiophosphonoacetate internucleotide linkage (see for example Sheehan et al., 2003, *Nucleic Acids Research*, 31, 4109-4118).

The chemically-modified internucleotide linkages having Formula I, for example, wherein any Z, W, X, and/or Y independently comprises a sulphur atom, can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) chemically-modified internucleotide linkages having Formula I at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified internucleotide linkages having Formula I at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine

nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In another embodiment, a siNA molecule of the invention having internucleotide linkage(s) of Formula I also comprises a chemically-modified nucleotide or non-nucleotide having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula II:

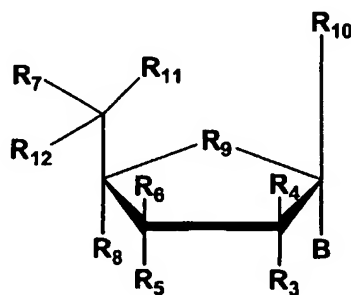


wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine,

pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula II can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula II at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 3'-end of the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula III:



20

wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-

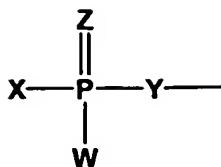
25

aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R<sub>9</sub> is O, S, CH<sub>2</sub>, S=O, CHF, or CF<sub>2</sub>, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be employed to be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine, pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula III can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (e.g., about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide(s) or non-nucleotide(s) of Formula III at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (e.g., about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end of the sense strand, the antisense strand, or both strands.

In another embodiment, a siNA molecule of the invention comprises a nucleotide having Formula II or III, wherein the nucleotide having Formula II or III is in an inverted configuration. For example, the nucleotide having Formula II or III is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a 5'-terminal phosphate group having Formula IV:



wherein each X and Y is independently O, S, N, alkyl, substituted alkyl, or alkylhalo; wherein each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, alkylhalo, or acetyl; and wherein W, X, Y and Z are not all O.

- 5 In one embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand, for example, a strand complementary to a target RNA, wherein the siNA molecule comprises an all RNA siNA molecule. In another embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand wherein the siNA molecule also comprises about 1 to about 3 (e.g., about 1, 2, or 3) nucleotide 3'-terminal nucleotide overhangs having about 1 to about 4 (e.g., about 1, 2, 3, or 4) deoxyribonucleotides on the 3'-end of one or both strands. In another embodiment, a 5'-terminal phosphate group having Formula IV is present on the target-complementary strand of a siNA molecule of the invention, for example a siNA molecule having chemical modifications having any of Formulae I-VII.

- In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more phosphorothioate internucleotide linkages. For example, in a non-limiting example, the invention features a chemically-modified short interfering nucleic acid (siNA) having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in one siNA strand. In yet another embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) individually having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in both siNA strands. The phosphorothioate internucleotide linkages can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more phosphorothioate internucleotide linkages at the 3'-end, the 5'-end, or both of the 3'- and

5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the sense strand comprises about 1 to about 5, specifically about 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) 2'-deoxy,

2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5 or more, for example about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a siNA molecule, wherein the antisense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more

phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or  
5 more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or  
10 more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another  
15 embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5, for example about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both  
20 of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule having about 1 to about 5, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages in each strand of the siNA molecule.

In another embodiment, the invention features a siNA molecule comprising 2'-5'  
25 internucleotide linkages. The 2'-5' internucleotide linkage(s) can be at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of one or both siNA sequence strands. In addition, the 2'-5' internucleotide linkage(s) can be present at various other positions within one or both siNA sequence strands, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a pyrimidine nucleotide in one or both strands  
30 of the siNA molecule can comprise a 2'-5' internucleotide linkage, or about 1, 2, 3, 4, 5,



6, 7, 8, 9, 10, or more including every internucleotide linkage of a purine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage.

In another embodiment, a chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-  
5 modified, wherein each strand is about 18 to about 27 (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length, wherein the duplex has about 18 to about 23 (e.g., about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the chemical modification comprises a structure having any of Formulae I-VII. For example, an exemplary chemically-modified siNA molecule of the invention comprises a duplex having two  
10 strands, one or both of which can be chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein each strand consists of about 21 nucleotides, each having a 2-nucleotide 3'-terminal nucleotide overhang, and wherein the duplex has about 19 base pairs. In another embodiment, a siNA molecule of the invention comprises a single stranded hairpin structure, wherein the siNA is about 36  
15 to about 70 (e.g., about 36, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (e.g., about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having  
20 about 42 to about 50 (e.g., about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 19 base pairs and a 2-nucleotide 3'-terminal nucleotide overhang. In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif,  
25 wherein the loop portion of the siNA molecule is biodegradable. For example, a linear hairpin siNA molecule of the invention is designed such that degradation of the loop portion of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

30 In another embodiment, a siNA molecule of the invention comprises a hairpin structure, wherein the siNA is about 25 to about 50 (e.g., about 25, 26, 27, 28, 29, 30, 31,

32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 3 to about 23 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. In another embodiment, a linear hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 20 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms an asymmetric hairpin structure having about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, an asymmetric hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is

biodegradable. In another embodiment, an asymmetric hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 16 to about 25 (*e.g.*, about 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides in length, wherein the sense region is about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides in length, wherein the sense region and the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 18 to about 22 (*e.g.*, about 18, 19, 20, 21, or 22) nucleotides in length and wherein the sense region is about 3 to about 15 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) nucleotides in length, wherein the sense region the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. In another embodiment, the asymmetric double stranded siNA molecule can also have a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV).

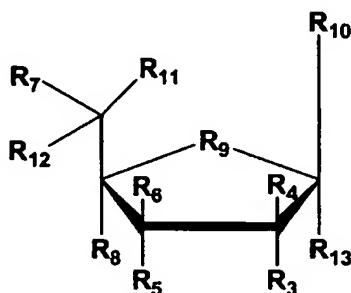
In another embodiment, a siNA molecule of the invention comprises a circular nucleic acid molecule, wherein the siNA is about 38 to about 70 (*e.g.*, about 38, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification, which comprises a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a circular oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof,

wherein the circular oligonucleotide forms a dumbbell shaped structure having about 19 base pairs and 2 loops.

In another embodiment, a circular siNA molecule of the invention contains two loop motifs, wherein one or both loop portions of the siNA molecule is biodegradable.

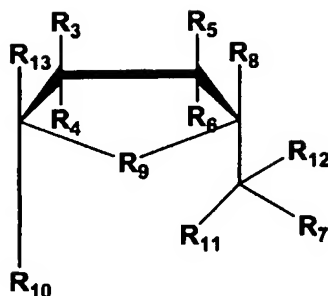
- 5 For example, a circular siNA molecule of the invention is designed such that degradation of the loop portions of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

- 10 In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) abasic moiety, for example a compound having Formula V:



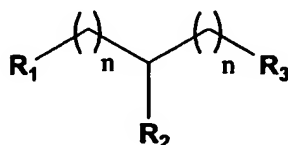
- 15 wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2.

- 20 In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) inverted abasic moiety, for example a compound having Formula VI:



wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and either R2, R3, R8 or R13 serve as points of attachment to the siNA molecule of the invention.

In another embodiment, a siNA molecule of the invention comprises at least one (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) substituted polyalkyl moieties, for example a compound having Formula VII:



wherein each n is independently an integer from 1 to 12, each R1, R2 and R3 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or a group having Formula I, and R1, R2 or R3 serves as points of attachment to the siNA molecule of the invention.

In another embodiment, the invention features a compound having Formula VII, wherein R1 and R2 are hydroxyl (OH) groups,  $n = 1$ , and R3 comprises O and is the point of attachment to the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both strands of a double-stranded siNA molecule of the invention or to a single-stranded siNA molecule of the invention. This modification is referred to herein as "glyceryl" (for example modification 6 in Figure 10).

In another embodiment, a moiety having any of Formula V, VI or VII of the invention is at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of a siNA molecule of the invention. For example, a moiety having Formula V, VI or VII can be present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense strand, the sense strand, or both antisense and sense strands of the siNA molecule. In addition, a moiety having Formula VII can be present at the 3'-end or the 5'-end of a hairpin siNA molecule as described herein.

In another embodiment, a siNA molecule of the invention comprises an abasic residue having Formula V or VI, wherein the abasic residue having Formula VI or VI is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) locked nucleic acid (LNA) nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In another embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) acyclic nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-

2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine

nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said antisense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or



more or all) purine nucleotides present in the antisense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering  
5 nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein  
any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are  
2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are  
2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine  
nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or  
10 more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine  
nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or  
alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering  
nucleic acid (siNA) molecule of the invention capable of mediating RNA interference  
15 (RNAi) against SARS inside a cell or reconstituted *in vitro* system comprising a sense  
region, wherein one or more pyrimidine nucleotides present in the sense region are 2'-  
deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-  
deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine  
nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine  
20 nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all  
purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine  
nucleotides are 2'-deoxy purine nucleotides), and an antisense region, wherein one or  
more pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro  
pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro  
25 pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-  
2'-fluoro pyrimidine nucleotides), and one or more purine nucleotides present in the  
antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides  
are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-  
O-methyl purine nucleotides). The sense region and/or the antisense region can have a  
30 terminal cap modification, such as any modification described herein or shown in Figure  
10, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the

sense and/or antisense sequence. The sense and/or antisense region can optionally further comprise a 3'-terminal nucleotide overhang having about 1 to about 4 (e.g., about 1, 2, 3, or 4) 2'-deoxynucleotides. The overhang nucleotides can further comprise one or more (e.g., about 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages. Non-limiting examples of these chemically-modified siNAs are shown in Figures 4 and 5 and Tables III and IV herein. In any of these described embodiments, the purine nucleotides present in the sense region are alternatively 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides) and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Also, in any of these embodiments, one or more purine nucleotides present in the sense region are alternatively purine ribonucleotides (e.g., wherein all purine nucleotides are purine ribonucleotides or alternately a plurality of purine nucleotides are purine ribonucleotides) and any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Additionally, in any of these embodiments, one or more purine nucleotides present in the sense region and/or present in the antisense region are alternatively selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides (e.g., wherein all purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides or alternately a plurality of purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides).

In another embodiment, any modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, comprise modified nucleotides having properties or characteristics similar to naturally occurring

ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, are resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi. Non-limiting examples of nucleotides having a northern configuration include locked nucleic acid (LNA) nucleotides (e.g., 2'-O, 4'-C-methylene-(D-ribofuranosyl) nucleotides); 2'-methoxyethoxy (MOE) nucleotides; 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro nucleotides, 2'-deoxy-2'-chloro nucleotides, 2'-azido nucleotides, and 2'-O-methyl nucleotides.

In one embodiment, the sense strand of a double stranded siNA molecule of the invention comprises a terminal cap moiety, (see for example Figure 10) such as an inverted deoxyabaisc moiety, at the 3'-end, 5'-end, or both 3' and 5'-ends of the sense strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid molecule (siNA) capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a conjugate covalently attached to the chemically-modified siNA molecule. Non-limiting examples of conjugates contemplated by the invention include conjugates and ligands described in Vargeese *et al.*, USSN 10/427,160, filed April 30, 2003, incorporated by reference herein in its entirety, including the drawings. In another embodiment, the conjugate is covalently attached to the chemically-modified siNA molecule via a biodegradable linker. In one embodiment, the conjugate molecule is attached at the 3'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In another embodiment, the conjugate molecule is attached at the 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In yet another embodiment, the conjugate molecule is attached both the 3'-end and 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule, or any

combination thereof. In one embodiment, a conjugate molecule of the invention comprises a molecule that facilitates delivery of a chemically-modified siNA molecule into a biological system, such as a cell. In another embodiment, the conjugate molecule attached to the chemically-modified siNA molecule is a polyethylene glycol, human  
5 serum albumin, or a ligand for a cellular receptor that can mediate cellular uptake. Examples of specific conjugate molecules contemplated by the instant invention that can be attached to chemically-modified siNA molecules are described in Vargeese *et al.*, U.S. Serial No. 10/201,394, filed July 22, 2002, incorporated by reference herein. The type of conjugates used and the extent of conjugation of siNA molecules of the invention  
10 can be evaluated for improved pharmacokinetic profiles, bioavailability, and/or stability of siNA constructs while at the same time maintaining the ability of the siNA to mediate RNAi activity. As such, one skilled in the art can screen siNA constructs that are modified with various conjugates to determine whether the siNA conjugate complex possesses improved properties while maintaining the ability to mediate RNAi, for  
15 example in animal models as are generally known in the art.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule of the invention, wherein the siNA further comprises a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the siNA to the antisense region of the siNA. In one embodiment, a nucleotide linker of the  
20 invention can be a linker of  $\geq 2$  nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length. In another embodiment, the nucleotide linker can be a nucleic acid aptamer. By "aptamer" or "nucleic acid aptamer" as used herein is meant a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that comprises a sequence recognized by the target molecule  
25 in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule where the target molecule does not naturally bind to a nucleic acid. The target molecule can be any molecule of interest. For example, the aptamer can be used to bind to a ligand-binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. This is a non-limiting example and those  
30 in the art will recognize that other embodiments can be readily generated using techniques generally known in the art. (See, for example, Gold *et al.*, 1995, *Annu. Rev. Biochem.*, 64, 763; Brody and Gold, 2000, *J. Biotechnol.*, 74, 5; Sun, 2000, *Curr. Opin.*

*Mol. Ther.*, 2, 100; Kusser, 2000, *J. Biotechnol.*, 74, 27; Hermann and Patel, 2000, *Science*, 287, 820; and Jayasena, 1999, *Clinical Chemistry*, 45, 1628.)

In yet another embodiment, a non-nucleotide linker of the invention comprises abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric compounds (e.g. polyethylene glycols such as those having between 2 and 100 ethylene glycol units). Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, 18:6353 and *Nucleic Acids Res.* 1987, 15:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, 113:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, 113:5109; Ma *et al.*, *Nucleic Acids Res.* 1993, 21:2585 and *Biochemistry* 1993, 32:1751; Durand *et al.*, *Nucleic Acids Res.* 1990, 18:6353; McCurdy *et al.*, *Nucleosides & Nucleotides* 1991, 10:287; Jschke *et al.*, *Tetrahedron Lett.* 1993, 34:301; Ono *et al.*, *Biochemistry* 1991, 30:9914; Arnold *et al.*, International Publication No. WO 89/02439; Usman *et al.*, International Publication No. WO 95/06731; Dudycz *et al.*, International Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc.* 1991, 113:4000, all hereby incorporated by reference herein. A "non-nucleotide" further means any group or compound that can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine, for example at the C1 position of the sugar.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) inside a cell or reconstituted *in vitro* system, wherein one or both strands of the siNA molecule that are assembled from two separate oligonucleotides do not comprise any ribonucleotides. For example, a siNA molecule can be assembled from a single oligonucleotide where the sense and antisense regions of the siNA comprise separate oligonucleotides not having any ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotides. In another example, a siNA molecule can be assembled from a single oligonucleotide where the sense and antisense regions of the siNA are linked or circularized by a nucleotide or non-nucleotide linker as described herein, wherein the oligonucleotide does not have any

ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotide. Applicant has surprisingly found that the presence of ribonucleotides (e.g., nucleotides having a 2'-hydroxyl group) within the siNA molecule is not required or essential to support RNAi activity. As such, in one embodiment, all positions within the siNA can include chemically modified nucleotides and/or non-nucleotides such as nucleotides and or non-nucleotides having Formula I, II, III, IV, V, VI, or VII or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group and a 3'-terminal phosphate group (e.g., a 2',3'-cyclic phosphate). In another embodiment, the single stranded siNA molecule of the invention comprises about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29) nucleotides. In yet another embodiment, the single stranded siNA molecule of the invention comprises one or more chemically modified nucleotides or non-nucleotides described herein. For example, all the positions within the siNA molecule can include chemically-modified nucleotides such as nucleotides having any of Formulae I-VII, or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence, wherein one or more pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine

nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and a terminal cap modification, such as any modification described herein or shown in Figure 10, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense sequence. The siNA  
5 optionally further comprises about 1 to about 4 or more (e.g., about 1, 2, 3, 4 or more) terminal 2'-deoxynucleotides at the 3'-end of the siNA molecule, wherein the terminal nucleotides can further comprise one or more (e.g., 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages, and wherein the siNA optionally further comprises a terminal phosphate group, such as a 5'-terminal  
10 phosphate group. In any of these embodiments, any purine nucleotides present in the antisense region are alternatively 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA (i.e., purine nucleotides present in the sense  
15 and/or antisense region) can alternatively be locked nucleic acid (LNA) nucleotides (e.g., wherein all purine nucleotides are LNA nucleotides or alternately a plurality of purine nucleotides are LNA nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA are alternatively 2'-methoxyethyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-methoxyethyl purine nucleotides or  
20 alternately a plurality of purine nucleotides are 2'-methoxyethyl purine nucleotides). In another embodiment, any modified nucleotides present in the single stranded siNA molecules of the invention comprise modified nucleotides having properties or characteristics similar to naturally occurring ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation  
25 (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the single stranded siNA molecules of the invention are preferably resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi.

In one embodiment, the invention features a method for modulating the expression  
30 of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the

siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

5 In one embodiment, the invention features a method for modulating the expression of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

10 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

15 In another embodiment, the invention features a method for modulating the expression of two or more SARS genes within a cell comprising: (a) synthesizing one or more siNA molecules of the invention, which can be chemically-modified, wherein the siNA strands comprise sequences complementary to RNA of the SARS genes and wherein the sense strand sequences of the siNAs comprise sequences identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

20 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA



molecule into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

In one embodiment, siNA molecules of the invention are used as reagents in *ex vivo* applications. For example, siNA reagents are introduced into tissue or cells that are transplanted into a subject for therapeutic effect. The cells and/or tissue can be derived from an organism or subject that later receives the explant, or can be derived from another organism or subject prior to transplantation. The siNA molecules can be used to modulate the expression of one or more genes in the cells or tissue, such that the cells or tissue obtain a desired phenotype or are able to perform a function when transplanted in vivo. In one embodiment, certain target cells from a patient are extracted. These extracted cells are contacted with siNAs targeting a specific nucleotide sequence within the cells under conditions suitable for uptake of the siNAs by these cells (e.g. using delivery reagents such as cationic lipids, liposomes and the like or using techniques such as electroporation to facilitate the delivery of siNAs into cells). The cells are then reintroduced back into the same patient or other patients. In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate

the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

5        In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular  
10        organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS genes in that organism.

15        In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of  
20        the SARS gene in the organism. The level of SARS protein or RNA can be determined as is known in the art.

      In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the  
25        siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism. The level of SARS protein or RNA can be determined as is known in the art.

      In one embodiment, the invention features a method for modulating the expression  
30        of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the

invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

5 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) contacting the cell in vitro or in vivo with the siNA molecule under  
10 conditions suitable to modulate the expression of the SARS genes in the cell.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b)  
15 contacting the cell of the tissue explant derived from a particular organism with the siNA molecule under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that  
20 organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS  
25 gene; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS  
30 genes in that organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b)  
5 introducing the siNA molecule into the organism under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA  
10 comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising contacting the organism with a siNA  
15 molecule of the invention under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising contacting the organism with one or more siNA molecules of the invention under conditions suitable to  
20 modulate the expression of the SARS genes in the organism.

The siNA molecules of the invention can be designed to down regulate or inhibit target (e.g., SARS) gene expression through RNAi targeting of a variety of RNA molecules. In one embodiment, the siNA molecules of the invention are used to target various RNAs corresponding to a target gene. Non-limiting examples of such RNAs  
25 include messenger RNA (mRNA), alternate RNA splice variants of target gene(s), post-transcriptionally modified RNA of target gene(s), pre-mRNA of target gene(s), and/or RNA templates. If alternate splicing produces a family of transcripts that are distinguished by usage of appropriate exons, the instant invention can be used to inhibit gene expression through the appropriate exons to specifically inhibit or to distinguish  
30 among the functions of gene family members. For example, a protein that contains an

alternatively spliced transmembrane domain can be expressed in both membrane bound and secreted forms. Use of the invention to target the exon containing the transmembrane domain can be used to determine the functional consequences of pharmaceutical targeting of membrane bound as opposed to the secreted form of the protein. Non-limiting examples of applications of the invention relating to targeting these RNA molecules include therapeutic pharmaceutical applications, pharmaceutical discovery applications, molecular diagnostic and gene function applications, and gene mapping, for example using single nucleotide polymorphism mapping with siNA molecules of the invention. Such applications can be implemented using known gene sequences or from partial sequences available from an expressed sequence tag (EST).

In another embodiment, the siNA molecules of the invention are used to target conserved sequences corresponding to a gene family or gene families such as SARS family genes. As such, siNA molecules targeting multiple SARS targets can provide increased therapeutic effect. In addition, siNA can be used to characterize pathways of gene function in a variety of applications. For example, the present invention can be used to inhibit the activity of target gene(s) in a pathway to determine the function of uncharacterized gene(s) in gene function analysis, mRNA function analysis, or translational analysis. The invention can be used to determine potential target gene pathways involved in various diseases and conditions toward pharmaceutical development. The invention can be used to understand pathways of gene expression involved in, for example, the progression and/or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue.

In one embodiment, siNA molecule(s) and/or methods of the invention are used to down regulate the expression of gene(s) that encode RNA referred to by Genbank Accession, for example SARS genes encoding RNA sequence(s) referred to herein by Genbank Accession number, for example, Genbank Accession Nos. shown in Table I.

In one embodiment, the invention features a method comprising: (a) generating a library of siNA constructs having a predetermined complexity; and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target RNA sequence. In one embodiment, the siNA molecules of (a) have strands of

a fixed length, for example, about 23 nucleotides in length. In another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described  
5 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the  
10 art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In one embodiment, the invention features a method comprising: (a) generating a randomized library of siNA constructs having a predetermined complexity, such as of  $4^N$ , where N represents the number of base paired nucleotides in each of the siNA construct  
15 strands (eg. for a siNA construct having 21 nucleotide sense and antisense strands with 19 base pairs, the complexity would be  $4^{19}$ ); and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target SARS RNA sequence. In another embodiment, the siNA molecules of (a) have strands of a fixed length, for example about 23 nucleotides in length. In yet another embodiment, the  
20 siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described in Example 7 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of SARS RNA are  
25 analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target SARS RNA sequence. The target SARS RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

30 In another embodiment, the invention features a method comprising: (a) analyzing the sequence of a RNA target encoded by a target gene; (b) synthesizing one or more sets

of siNA molecules having sequence complementary to one or more regions of the RNA of (a); and (c) assaying the siNA molecules of (b) under conditions suitable to determine RNAi targets within the target RNA sequence. In one embodiment, the siNA molecules of (b) have strands of a fixed length, for example about 23 nucleotides in length. In another embodiment, the siNA molecules of (b) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. Fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by expression in *in vivo* systems.

By "target site" is meant a sequence within a target RNA that is "targeted" for cleavage mediated by a siNA construct which contains sequences within its antisense region that are complementary to the target sequence.

By "detectable level of cleavage" is meant cleavage of target RNA (and formation of cleaved product RNAs) to an extent sufficient to discern cleavage products above the background of RNAs produced by random degradation of the target RNA. Production of cleavage products from 1-5% of the target RNA is sufficient to detect above the background for most methods of detection.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a method for diagnosing a disease or condition in a subject comprising administering to the subject a composition of the invention under conditions suitable for the diagnosis of the disease or condition in the subject. In another embodiment, the invention features a method for

treating or preventing a disease or condition in a subject, comprising administering to the subject a composition of the invention under conditions suitable for the treatment or prevention of the disease or condition in the subject, alone or in conjunction with one or more other therapeutic compounds. In yet another embodiment, the invention features a method for reducing or preventing tissue rejection in a subject comprising administering to the subject a composition of the invention under conditions suitable for the reduction or prevention of tissue rejection in the subject.

In another embodiment, the invention features a method for validating a SARS gene target, comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a cell, tissue, or organism under conditions suitable for modulating expression of the SARS target gene in the cell, tissue, or organism; and (c) determining the function of the gene by assaying for any phenotypic change in the cell, tissue, or organism.

In another embodiment, the invention features a method for validating a SARS target comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a biological system under conditions suitable for modulating expression of the SARS target gene in the biological system; and (c) determining the function of the gene by assaying for any phenotypic change in the biological system.

By "biological system" is meant, material, in a purified or unpurified form, from biological sources, including but not limited to human or animal, wherein the system comprises the components required for RNAi activity. The term "biological system" includes, for example, a cell, tissue, or organism, or extract thereof. The term biological system also includes reconstituted RNAi systems that can be used in an *in vitro* setting.

By "phenotypic change" is meant any detectable change to a cell that occurs in response to contact or treatment with a nucleic acid molecule of the invention (e.g., siNA). Such detectable changes include, but are not limited to, changes in shape, size, proliferation, motility, protein expression or RNA expression or other physical or



chemical changes as can be assayed by methods known in the art. The detectable change can also include expression of reporter genes/molecules such as Green Florescent Protein (GFP) or various tags that are used to identify an expressed protein or any other cellular component that can be assayed.

5        In one embodiment, the invention features a kit containing a siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the expression of a SARS target gene in a biological system, including, for example, in a cell, tissue, or organism. In another embodiment, the invention features a kit containing more than one siNA molecule of the invention, which can be chemically-modified, that  
10       can be used to modulate the expression of more than one SARS target gene in a biological system, including, for example, in a cell, tissue, or organism.

      In one embodiment, the invention features a cell containing one or more siNA molecules of the invention, which can be chemically-modified. In another embodiment, the cell containing a siNA molecule of the invention is a mammalian cell. In yet another  
15       embodiment, the cell containing a siNA molecule of the invention is a human cell.

      In one embodiment, the synthesis of a siNA molecule of the invention, which can be chemically-modified, comprises: (a) synthesis of two complementary strands of the siNA molecule; (b) annealing the two complementary strands together under conditions suitable to obtain a double-stranded siNA molecule. In another embodiment, synthesis  
20       of the two complementary strands of the siNA molecule is by solid phase oligonucleotide synthesis. In yet another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase tandem oligonucleotide synthesis.

      In one embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing a first oligonucleotide sequence strand of  
25       the siNA molecule, wherein the first oligonucleotide sequence strand comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of the second oligonucleotide sequence strand of the siNA; (b) synthesizing the second oligonucleotide sequence strand of siNA on the scaffold of the first oligonucleotide sequence strand, wherein the second oligonucleotide sequence strand further comprises a chemical moiety  
30       than can be used to purify the siNA duplex; (c) cleaving the linker molecule of (a) under

conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex; and (d) purifying the siNA duplex utilizing the chemical moiety of the second oligonucleotide sequence strand. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions using an alkylamine base such as methylamine. In one embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place concomitantly. In another embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group, which can be employed in a trityl-on synthesis strategy as described herein. In yet another embodiment, the chemical moiety, such as a dimethoxytrityl group, is removed during purification, for example, using acidic conditions.

In a further embodiment, the method for siNA synthesis is a solution phase synthesis or hybrid phase synthesis wherein both strands of the siNA duplex are synthesized in tandem using a cleavable linker attached to the first sequence which acts a scaffold for synthesis of the second sequence. Cleavage of the linker under conditions suitable for hybridization of the separate siNA sequence strands results in formation of the double-stranded siNA molecule.

In another embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing one oligonucleotide sequence strand of the siNA molecule, wherein the sequence comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of another oligonucleotide sequence; (b) synthesizing a second oligonucleotide sequence having complementarity to the first sequence strand on the scaffold of (a), wherein the second sequence comprises the other strand of the double-stranded siNA molecule and wherein the second sequence further comprises a chemical moiety than can be used to isolate the attached oligonucleotide

sequence; (c) purifying the product of (b) utilizing the chemical moiety of the second oligonucleotide sequence strand under conditions suitable for isolating the full-length sequence comprising both siNA oligonucleotide strands connected by the cleavable linker and under conditions suitable for the two siNA oligonucleotide strands to  
5 hybridize and form a stable duplex. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions. In another embodiment, cleavage of the linker molecule in (c) above takes place after deprotection of the oligonucleotide. In another embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled  
10 pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity or differing reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place  
15 either concomitantly or sequentially. In one embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group.

In another embodiment, the invention features a method for making a double-stranded siNA molecule in a single synthetic process comprising: (a) synthesizing an  
20 oligonucleotide having a first and a second sequence, wherein the first sequence is complementary to the second sequence, and the first oligonucleotide sequence is linked to the second sequence via a cleavable linker, and wherein a terminal 5'-protecting group, for example, a 5'-O-dimethoxytrityl group (5'-O-DMT) remains on the oligonucleotide having the second sequence; (b) deprotecting the oligonucleotide whereby the  
25 deprotection results in the cleavage of the linker joining the two oligonucleotide sequences; and (c) purifying the product of (b) under conditions suitable for isolating the double-stranded siNA molecule, for example using a trityl-on synthesis strategy as described herein.

In another embodiment, the method of synthesis of siNA molecules of the  
30 invention comprises the teachings of Scaringe *et al.*, US Patent Nos. 5,889,136; 6,008,400; and 6,111,086, incorporated by reference herein in their entirety.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications, for example, one or more chemical modifications having any of Formulae I-VII or any combination thereof that increases the nuclease resistance of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased nuclease resistance comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased nuclease resistance.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the sense and antisense strands of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the sense and antisense strands of the siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the sense and antisense strands of the siNA molecule.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target RNA sequence within a cell.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target DNA sequence within a cell.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulate the polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA construct.

In another embodiment, the invention features a method for generating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to a chemically-modified siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA molecule.

In one embodiment, the invention features chemically-modified siNA constructs that mediate RNAi against SARS in a cell, wherein the chemical modifications do not

significantly effect the interaction of siNA with a target RNA molecule, DNA molecule and/or proteins or other factors that are essential for RNAi in a manner that would decrease the efficacy of RNAi mediated by such siNA constructs.

5 In another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity.

10 In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS target RNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target RNA.

15 In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS target DNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target DNA.

20 In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the cellular uptake of the siNA construct.

25 In another embodiment, the invention features a method for generating siNA molecules against SARS with improved cellular uptake comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved cellular uptake.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that increases the bioavailability of the siNA construct,

for example, by attaching polymeric conjugates such as polyethyleneglycol or equivalent conjugates that improve the pharmacokinetics of the siNA construct, or by attaching conjugates that target specific tissue types or cell types *in vivo*. Non-limiting examples of such conjugates are described in Vargeese *et al.*, U.S. Serial No. 10/201,394  
5 incorporated by reference herein.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability, comprising (a) introducing a conjugate into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved  
10 bioavailability. Such conjugates can include ligands for cellular receptors, such as peptides derived from naturally occurring protein ligands; protein localization sequences, including cellular ZIP code sequences; antibodies; nucleic acid aptamers; vitamins and other co-factors, such as folate and N-acetylgalactosamine; polymers, such as polyethyleneglycol (PEG); phospholipids; cholesterol; polyamines, such as spermine or  
15 spermidine; and others.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically  
20 modified in a manner that it can no longer act as a guide sequence for efficiently mediating RNA interference and/or be recognized by cellular proteins that facilitate RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary  
25 to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein the second sequence is designed or modified in a manner that prevents its entry into the RNAi pathway as a guide sequence or as a sequence that is complementary to a target nucleic acid (e.g., RNA) sequence. Such design or modifications are expected to enhance the activity of siNA and/or  
30 improve the specificity of siNA molecules of the invention. These modifications are also expected to minimize any off-target effects and/or associated toxicity.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is incapable of  
5 acting as a guide sequence for mediating RNA interference.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence does not have a  
10 terminal 5'-hydroxyl (5'-OH) or 5'-phosphate group.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a  
15 terminal cap moiety at the 5'-end of said second sequence. In one embodiment, the terminal cap moiety comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in Figure 10, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a  
20 terminal cap moiety at the 5'-end and 3'-end of said second sequence. In one  
25 embodiment, each terminal cap moiety individually comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in Figure 10, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a method for generating siNA  
30 molecules of the invention with improved specificity for down regulating or inhibiting



the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising (a) introducing one or more chemical modifications into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved specificity. In

5 another embodiment, the chemical modification used to improve specificity comprises terminal cap modifications at the 5'-end, 3'-end, or both 5' and 3'-ends of the siNA molecule. The terminal cap modifications can comprise, for example, structures shown in Figure 10 (e.g. inverted deoxybasic moieties) or any other chemical modification that renders a portion of the siNA molecule (e.g. the sense strand) incapable of mediating

10 RNA interference against an off target nucleic acid sequence. In a non-limiting example, a siNA molecule is designed such that only the antisense sequence of the siNA molecule can serve as a guide sequence for RISC mediated degradation of a corresponding target RNA sequence. This can be accomplished by rendering the sense sequence of the siNA inactive by introducing chemical modifications to the sense strand that preclude

15 recognition of the sense strand as a guide sequence by RNAi machinery. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand of the siNA, or any other group that serves to render the sense strand inactive as a guide sequence for mediating RNA interference. These modifications, for example, can result in a molecule where the 5'-end of the sense strand no longer has a

20 free 5'-hydroxyl (5'-OH) or a free 5'-phosphate group (e.g., phosphate, diphosphate, triphosphate, cyclic phosphate etc.). Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

25 In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising introducing one or more chemical modifications into the structure of a siNA molecule that prevent a strand or portion of the siNA molecule

30 from acting as a template or guide sequence for RNAi activity. In one embodiment, the inactive strand or sense region of the siNA molecule is the sense strand or sense region of the siNA molecule, i.e. the strand or region of the siNA that does not have

complementarity to the target nucleic acid sequence. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand or region of the siNA that does not comprise a 5'-hydroxyl (5'-OH) or 5'-phosphate group, or any other group that serves to render the sense strand or sense region inactive as a guide  
5 sequence for mediating RNA interference. Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for screening siNA molecules  
10 that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of unmodified siNA molecules, (b) screening the siNA molecules of step (a) under conditions suitable for isolating siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence, and  
15 (c) introducing chemical modifications (e.g. chemical modifications as described herein or as otherwise known in the art) into the active siNA molecules of (b). In one embodiment, the method further comprises re-screening the chemically modified siNA molecules of step (c) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

20 In one embodiment, the invention features a method for screening chemically modified siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of chemically modified siNA molecules (e.g. siNA molecules as described herein or as otherwise known in the art), and (b) screening the siNA molecules of step (a) under conditions suitable for isolating  
25 chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

The term "ligand" refers to any compound or molecule, such as a drug, peptide, hormone, or neurotransmitter, that is capable of interacting with another compound, such as a receptor, either directly or indirectly. The receptor that interacts with a ligand can be  
30 present on the surface of a cell or can alternately be an intercellular receptor. Interaction

of the ligand with the receptor can result in a biochemical reaction, or can simply be a physical interaction or association.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing an excipient formulation to a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability. Such excipients include polymers such as cyclodextrins, lipids, cationic lipids, polyamines, phospholipids, nanoparticles, receptors, ligands, and others.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing nucleotides having any of Formulae I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability.

In another embodiment, polyethylene glycol (PEG) can be covalently attached to siNA compounds of the present invention. The attached PEG can be any molecular weight, preferably from about 2,000 to about 50,000 daltons (Da).

The present invention can be used alone or as a component of a kit having at least one of the reagents necessary to carry out the *in vitro* or *in vivo* introduction of RNA to test samples and/or subjects. For example, preferred components of the kit include a siNA molecule of the invention and a vehicle that promotes introduction of the siNA into cells of interest as described herein (e.g., using lipids and other methods of transfection known in the art, see for example Beigelman *et al*, US 6,395,713). The kit can be used for target validation, such as in determining gene function and/or activity, or in drug optimization, and in drug discovery (see for example Usman *et al.*, USSN 60/402,996). Such a kit can also include instructions to allow a user of the kit to practice the invention.

The term "short interfering nucleic acid", "siNA", "short interfering RNA", "siRNA", "short interfering nucleic acid molecule", "short interfering oligonucleotide molecule", or "chemically-modified short interfering nucleic acid molecule" as used herein refers to any nucleic acid molecule capable of inhibiting or down regulating gene

expression or viral replication, for example by mediating RNA interference "RNAi" or gene silencing in a sequence-specific manner; see for example Zamore *et al.*, 2000, *Cell*, 101, 25-33; Bass, 2001, *Nature*, 411, 428-429; Elbashir *et al.*, 2001, *Nature*, 411, 494-498; and Kreutzer *et al.*, International PCT Publication No. WO 00/44895; Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.*, International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO 01/29058; Deschamps-Dépaillette, International PCT Publication No. WO 99/07409; and Li *et al.*, International PCT Publication No. WO 00/44914; Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237; Hutvagner and Zamore, 2002, *Science*, 297, 2056-60; McManus *et al.*, 2002, *RNA*, 8, 842-850; Reinhart *et al.*, 2002, *Gene & Dev.*, 16, 1616-1626; and Reinhart & Bartel, 2002, *Science*, 297, 1831). Non limiting examples of siNA molecules of the invention are shown in Figures 4-6, and Tables II and III herein. For example the siNA can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double stranded structure, for example wherein the double stranded region is about 19 base pairs); the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. Alternatively, the siNA is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s). The siNA can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having

self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The

5 siNA can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a

10 portion thereof, and wherein the circular polynucleotide can be processed either *in vivo* or *in vitro* to generate an active siNA molecule capable of mediating RNAi. The siNA can also comprise a single stranded polynucleotide having nucleotide sequence complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof (for example, where such siNA molecule does not require the presence within the

15 siNA molecule of nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide can further comprise a terminal phosphate group, such as a 5'-phosphate (see for example Martinez *et al.*, 2002, *Cell.*, 110, 563-574 and Schwarz *et al.*, 2002, *Molecular Cell*, 10, 537-568), or 5',3'-diphosphate. In certain embodiments, the siNA molecule of the invention comprises

20 separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic interactions, and/or stacking interactions. In certain embodiments, the siNA molecules of the invention comprise

25 nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the siNA molecule of the invention interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene. As used herein, siNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically-modified nucleotides and non-

30 nucleotides. In certain embodiments, the short interfering nucleic acid molecules of the invention lack 2'-hydroxy (2'-OH) containing nucleotides. Applicant describes in certain embodiments short interfering nucleic acids that do not require the presence of

nucleotides having a 2'-hydroxy group for mediating RNAi and as such, short interfering nucleic acid molecules of the invention optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such siNA molecules that do not require the presence of ribonucleotides within the siNA molecule to support RNAi can however  
5 have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, siNA molecules can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. The modified short interfering nucleic acid molecules of the invention can also be referred to as short interfering modified oligonucleotides "siMON."

10 As used herein, the term siNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically-modified  
15 siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, siNA molecules of the invention can be used to epigenetically silence genes at both the post-transcriptional level or the  
20 pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siNA molecules of the invention can result from siNA mediated modification of chromatin structure to alter gene expression (see, for example, Verdel *et al.*, 2004, *Science*, 303, 672-676; Pal-Bhadra *et al.*, 2004, *Science*, 303, 669-672; Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-  
25 2237).

In one embodiment, a siNA molecule of the invention is a duplex forming oligonucleotide "DFO", (see for example Figures 14-15 and Vaish *et al.*, USSN 10/727,780 filed December 3, 2003).

30 In one embodiment, a siNA molecule of the invention is a multifunctional siNA, (see for example Figures 16-22 and Jadhav *et al.*, USSN 60/543,480, filed February 10,

2004). The multifunctional siNA of the invention can comprise sequence targeting, for example, two regions of SARS RNA (see for example target sequences in Tables II and III) or alternately, SARS RNA and cellular RNA involved in SARS virus infection or replication. In another embodiment, a multifunctional siNA of the invention can  
5 comprise sequence targeting for example both viral genes encoding RNAi inhibitory factors and viral genes encoding viral structural proteins.

By "asymmetric hairpin" as used herein is meant a linear siNA molecule comprising an antisense region, a loop portion that can comprise nucleotides or non-nucleotides, and a sense region that comprises fewer nucleotides than the antisense  
10 region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex with loop. For example, an asymmetric hairpin siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g., about 19, 20, 21, or 22) nucleotides) and a loop region comprising about 4 to about 8  
15 (e.g., about 4, 5, 6, 7, or 8) nucleotides, and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region. The asymmetric hairpin siNA molecule can also comprise a 5'-terminal phosphate group that can be chemically modified. The loop portion of the asymmetric hairpin siNA molecule can comprise nucleotides, non-  
20 nucleotides, linker molecules, or conjugate molecules as described herein.

By "asymmetric duplex" as used herein is meant a siNA molecule having two separate strands comprising a sense region and an antisense region, wherein the sense region comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and  
25 form a duplex. For example, an asymmetric duplex siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g. about 19, 20, 21, or 22) nucleotides) and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region.

30 By "modulate" is meant that the expression of the gene, or level of RNA molecule or equivalent RNA molecules encoding one or more proteins or protein subunits, or

activity of one or more proteins or protein subunits is up regulated or down regulated, such that expression, level, or activity is greater than or less than that observed in the absence of the modulator. For example, the term "modulate" can mean "inhibit," but the use of the word "modulate" is not limited to this definition.

5 By "inhibit", "down-regulate", or "reduce", it is meant that the expression of the gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, is reduced below that observed in the absence of the nucleic acid molecules (e.g., siNA) of the invention. In one embodiment, inhibition, down-regulation or reduction with an siNA  
10 molecule is below that level observed in the presence of an inactive or attenuated molecule. In another embodiment, inhibition, down-regulation, or reduction with siNA molecules is below that level observed in the presence of, for example, an siNA molecule with scrambled sequence or with mismatches. In another embodiment, inhibition, down-regulation, or reduction of gene expression with a nucleic acid molecule  
15 of the instant invention is greater in the presence of the nucleic acid molecule than in its absence.

By "gene", or "target gene", is meant, a nucleic acid that encodes an RNA, for example, nucleic acid sequences including, but not limited to, structural genes encoding a polypeptide. A gene or target gene can also encode a functional RNA (fRNA) or non-  
20 coding RNA (ncRNA), such as small temporal RNA (stRNA), micro RNA (miRNA), small nuclear RNA (snRNA), short interfering RNA (siRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and precursor RNAs thereof. Such non-coding RNAs can serve as target nucleic acid molecules for siNA mediated RNA interference in modulating the activity of fRNA or ncRNA involved in functional  
25 or regulatory cellular processes. Abberant fRNA or ncRNA activity leading to disease can therefore be modulated by siNA molecules of the invention. siNA molecules targeting fRNA and ncRNA can also be used to manipulate or alter the genotype or phenotype of an organism or cell, by intervening in cellular processes such as genetic imprinting, transcription, translation, or nucleic acid processing (e.g., transamination, methylation etc.). The target gene can be a gene derived from a cell, an endogenous  
30 gene, a transgene, or exogenous genes such as genes of a pathogen, for example a virus,



which is present in the cell after infection thereof. The cell containing the target gene can be derived from or contained in any organism, for example a plant, animal, protozoan, virus, bacterium, or fungus. Non-limiting examples of plants include monocots, dicots, or gymnosperms. Non-limiting examples of animals include  
5 vertebrates or invertebrates. Non-limiting examples of fungi include molds or yeasts.

By "SARS" or "SARS virus" as used herein is meant the SARS virus or any protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome. The term "SARS" also includes nucleic acid molecules encoding RNA or protein(s) associated with the development and/or maintenance of SARS virus infection,  
10 such as nucleic acid molecules which encode SARS RNA or polypeptides (such as polynucleotides having Genbank Accession numbers shown in Table I), including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as well as genes involved in SARS pathways of gene expression and/or SARS activity. Also, the term "SARS" is meant to encompass SARS viral gene products  
15 and genes that modulate cellular targets for SARS virus infection, such as those described herein.

By "SARS protein" or "SARS virus protein" is meant, protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome or alternately, cellular proteins involved in SARS virus infection and/or replication.

20 By "homologous sequence" is meant, a nucleotide sequence that is shared by one or more polynucleotide sequences, such as genes, gene transcripts and/or non-coding polynucleotides. For example, a homologous sequence can be a nucleotide sequence that is shared by two or more genes encoding related but different proteins, such as different members of a gene family, different protein epitopes, different protein isoforms or  
25 completely divergent genes, such as a cytokine and its corresponding receptors. A homologous sequence can be a nucleotide sequence that is shared by two or more non-coding polynucleotides, such as noncoding DNA or RNA, regulatory sequences, introns, and sites of transcriptional control or regulation. Homologous sequences can also include conserved sequence regions shared by more than one polynucleotide sequence.  
30 Homology does not need to be perfect homology (e.g., 100%), as partially homologous sequences are also contemplated by the instant invention (e.g., 99%, 98%, 97%, 96%,

95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80% etc.).

By "conserved sequence region" is meant, a nucleotide sequence of one or more regions in a polynucleotide does not vary significantly between generations or from one biological system or organism to another biological system or organism. The polynucleotide can include both coding and non-coding DNA and RNA.

By "sense region" is meant a nucleotide sequence of a siNA molecule having complementarity to an antisense region of the siNA molecule. In addition, the sense region of a siNA molecule can comprise a nucleic acid sequence having homology with a target nucleic acid sequence.

By "antisense region" is meant a nucleotide sequence of a siNA molecule having complementarity to a target nucleic acid sequence. In addition, the antisense region of a siNA molecule can optionally comprise a nucleic acid sequence having complementarity to a sense region of the siNA molecule.

By "target nucleic acid" is meant any nucleic acid sequence whose expression or activity is to be modulated. The target nucleic acid can be DNA or RNA.

By "complementarity" is meant that a nucleic acid can form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., RNAi activity. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner *et al.*, 1987, *CSH Symp. Quant. Biol.* LII pp.123-133; Frier *et al.*, 1986, *Proc. Nat. Acad. Sci. USA* 83:9373-9377; Turner *et al.*, 1987, *J. Am. Chem. Soc.* 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, or 10 nucleotides out of a total of 10 nucleotides in the first oligonucleotide being base paired to a second nucleic acid sequence having 10 nucleotides represents 50%, 60%, 70%, 80%, 90%, and

100% complementary respectively). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

5 The siNA molecules of the invention represent a novel therapeutic approach to treat various diseases and conditions, including SARS virus infection, acute respiratory failure, viral pneumonia, and any other indications that can respond to the level of SARS in a cell or tissue. The reduction of SARS expression and thus reduction in the level of the respective protein relieves, to some extent, the symptoms of the disease or condition.

10 In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently about 18 to about 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (*e.g.*, about 17, 18, 19, 20, 21, 22 or 23). In yet another embodiment, siNA molecules of the invention comprising hairpin or circular structures are about 35 to about 55 (*e.g.*, about 35, 40, 45, 50 or 55) nucleotides in length, or about 38 to about 44 (*e.g.*, 38, 39, 40, 41, 42, 43 or 44) nucleotides in length and comprising about 16 to about 22 (*e.g.*, about 16, 17, 18, 19, 20, 21 or 22) base pairs. Exemplary siNA molecules of the invention are shown in Table II. Exemplary synthetic siNA molecules of the invention are shown in Table III and/or Figures 4-5.

20 As used herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism, *e.g.*, specifically does not refer to a human. The cell can be present in an organism, *e.g.*, birds, plants and mammals such as humans, cows, sheep, apes, monkeys, swine, dogs, and cats. The cell can be prokaryotic (*e.g.*, bacterial cell) or eukaryotic (*e.g.*, mammalian or plant cell). The cell can be of somatic or germ line origin, totipotent or pluripotent, dividing or non-dividing. The cell can also be derived from or can comprise a gamete or embryo, a stem cell, or a fully differentiated cell.

30 The siNA molecules of the invention are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, infusion pump or stent, with or

without their incorporation in biopolymers. In particular embodiments, the nucleic acid molecules of the invention comprise sequences shown in Tables II-III and/or Figures 4-5. Examples of such nucleic acid molecules consist essentially of sequences defined in these tables and figures. Furthermore, the chemically modified constructs described in

5 Table IV can be applied to any siNA sequence of the invention.

In another aspect, the invention provides mammalian cells containing one or more siNA molecules of this invention. The one or more siNA molecules can independently be targeted to the same or different sites.

By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By

10 "ribonucleotide" is meant a nucleotide with a hydroxyl group at the 2' position of a  $\beta$ -D-ribo-furanose moiety. The terms include double-stranded RNA, single-stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more

15 nucleotides. Such alterations can include addition of non-nucleotide material, such as to the end(s) of the siNA or internally, for example at one or more nucleotides of the RNA. Nucleotides in the RNA molecules of the instant invention can also comprise non-standard nucleotides, such as non-naturally occurring nucleotides or chemically synthesized nucleotides or deoxynucleotides. These altered RNAs can be referred to as

20 analogs or analogs of naturally-occurring RNA.

By "subject" is meant an organism, which is a donor or recipient of explanted cells or the cells themselves. "Subject" also refers to an organism to which the nucleic acid molecules of the invention can be administered. A subject can be a mammal or mammalian cells, including a human or human cells.

25 The term "phosphorothioate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise a sulfur atom. Hence, the term phosphorothioate refers to both phosphorothioate and phosphorodithioate internucleotide linkages.

The term "phosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise an acetyl or protected acetyl group.

The term "thiophosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z comprises an acetyl or protected acetyl group and  
5 W comprises a sulfur atom or alternately W comprises an acetyl or protected acetyl group and Z comprises a sulfur atom.

The term "universal base" as used herein refers to nucleotide base analogs that form base pairs with each of the natural DNA/RNA bases with little discrimination between them. Non-limiting examples of universal bases include C-phenyl, C-naphthyl  
10 and other aromatic derivatives, inosine, azole carboxamides, and nitroazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole as known in the art (see for example Loakes, 2001, *Nucleic Acids Research*, 29, 2437-2447).

The term "acyclic nucleotide" as used herein refers to any nucleotide having an acyclic ribose sugar, for example where any of the ribose carbons (C1, C2, C3, C4, or  
15 C5), are independently or in combination absent from the nucleotide.

The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed herein (e.g., cancers and othe proliferative conditions). For example, to treat a particular disease or condition, the siNA molecules can be administered to a subject or can be  
20 administered to other appropriate cells evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

In a further embodiment, the siNA molecules can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules could be used in combination with one or more known therapeutic  
25 agents to treat a disease or condition. Non-limiting examples of other therapeutic agents that can be readily combined with a siNA molecule of the invention are enzymatic nucleic acid molecules, allosteric nucleic acid molecules, antisense, decoy, or aptamer nucleic acid molecules, antibodies such as monoclonal antibodies, small molecules, and other organic and/or inorganic compounds including metals, salts and ions.

In one embodiment, the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention, in a manner which allows expression of the siNA molecule. For example, the vector can contain sequence(s) encoding both strands of a siNA molecule comprising a duplex. The vector  
5 can also contain sequence(s) encoding a single nucleic acid molecule that is self-complementary and thus forms a siNA molecule. Non-limiting examples of such expression vectors are described in Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online  
10 publication doi:10.1038/nm725.

In another embodiment, the invention features a mammalian cell, for example, a human cell, including an expression vector of the invention.

In yet another embodiment, the expression vector of the invention comprises a sequence for a siNA molecule having complementarity to a RNA molecule referred to by  
15 a Genbank Accession numbers, for example Genbank Accession Nos. shown in Table I.

In one embodiment, an expression vector of the invention comprises a nucleic acid sequence encoding two or more siNA molecules, which can be the same or different.

In another aspect of the invention, siNA molecules that interact with target RNA molecules and down-regulate gene encoding target RNA molecules (for example target  
20 RNA molecules referred to by Genbank Accession numbers herein) are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as  
25 described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecules bind and down-regulate gene function or expression via RNA interference (RNAi). Delivery of siNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by  
30 administration to target cells ex-planted from a subject followed by reintroduction into

the subject, or by any other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

- 5 Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a non-limiting example of a scheme for the synthesis of siNA molecules. The complementary siNA sequence strands, strand 1 and strand 2, are synthesized in tandem and are connected by a cleavable linkage, such as a nucleotide succinate or abasic succinate, which can be the same or different from the cleavable linker used for solid phase synthesis on a solid support. The synthesis can be either solid phase or solution phase, in the example shown, the synthesis is a solid phase synthesis. The synthesis is performed such that a protecting group, such as a dimethoxytrityl group, remains intact on the terminal nucleotide of the tandem oligonucleotide. Upon cleavage and deprotection of the oligonucleotide, the two siNA strands spontaneously hybridize to form a siNA duplex, which allows the purification of the duplex by utilizing the properties of the terminal protecting group, for example by applying a trityl on purification method wherein only duplexes/oligonucleotides with the terminal protecting group are isolated.

Figure 2 shows a MALDI-TOF mass spectrum of a purified siNA duplex synthesized by a method of the invention. The two peaks shown correspond to the predicted mass of the separate siNA sequence strands. This result demonstrates that the siNA duplex generated from tandem synthesis can be purified as a single entity using a simple trityl-on purification methodology.

Figure 3 shows a non-limiting proposed mechanistic representation of target RNA degradation involved in RNAi. Double-stranded RNA (dsRNA), which is generated by RNA-dependent RNA polymerase (RdRP) from foreign single-stranded RNA, for example viral, transposon, or other exogenous RNA, activates the DICER enzyme that in

turn generates siNA duplexes. Alternately, synthetic or expressed siNA can be introduced directly into a cell by appropriate means. An active siNA complex forms which recognizes a target RNA, resulting in degradation of the target RNA by the RISC endonuclease complex or in the synthesis of additional RNA by RNA-dependent RNA polymerase (RdRP), which can activate DICER and result in additional siNA molecules, thereby amplifying the RNAi response.

Figure 4A-F shows non-limiting examples of chemically-modified siNA constructs of the present invention. In the figure, N stands for any nucleotide (adenosine, guanosine, cytosine, uridine, or optionally thymidine, for example thymidine can be substituted in the overhanging regions designated by parenthesis (N N). Various modifications are shown for the sense and antisense strands of the siNA constructs.

Figure 4A: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4B: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all



pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified  
5 internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the sense and antisense strand.

**Figure 4C:** The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and  
10 wherein all pyrimidine nucleotides that may be present are 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally  
15 complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as  
20 described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

**Figure 4D:** The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified  
25 nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the  
30 target RNA sequence, wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are

2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown  
5 as "s", optionally connects the (N N) nucleotides in the antisense strand.

**Figure 4E:** The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,  
10 deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are  
15 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

**Figure 4F:** The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,  
20 deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and having one 3'-terminal phosphorothioate internucleotide linkage and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro  
25 modified nucleotides and all purine nucleotides that may be present are 2'-deoxy nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,  
30 modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,

deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand. The antisense strand of constructs A-F comprise sequence complementary to any target nucleic acid sequence of the invention. Furthermore, when a glyceryl moiety (L) is present at the 3'-end of the antisense strand for any construct shown in Figure 4 A-F, the modified internucleotide linkage is optional.

Figure 5A-F shows non-limiting examples of specific chemically-modified siNA sequences of the invention. A-F applies the chemical modifications described in Figure 4A-F to a SARS virus siNA sequence. Such chemical modifications can be applied to any SARS sequence and/or SARS polymorphism sequence.

Figure 6 shows non-limiting examples of different siNA constructs of the invention. The examples shown (constructs 1, 2, and 3) have 19 representative base pairs; however, different embodiments of the invention include any number of base pairs described herein. Bracketed regions represent nucleotide overhangs, for example comprising about 1, 2, 3, or 4 nucleotides in length, preferably about 2 nucleotides. Constructs 1 and 2 can be used independently for RNAi activity. Construct 2 can comprise a polynucleotide or non-nucleotide linker, which can optionally be designed as a biodegradable linker. In one embodiment, the loop structure shown in construct 2 can comprise a biodegradable linker that results in the formation of construct 1 *in vivo* and/or *in vitro*. In another example, construct 3 can be used to generate construct 2 under the same principle wherein a linker is used to generate the active siNA construct 2 *in vivo* and/or *in vitro*, which can optionally utilize another biodegradable linker to generate the active siNA construct 1 *in vivo* and/or *in vitro*. As such, the stability and/or activity of the siNA constructs can be modulated based on the design of the siNA construct for use *in vivo* or *in vitro* and/or *in vitro*.

Figure 7A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate siNA hairpin constructs.

**Figure 7A:** A DNA oligomer is synthesized with a 5'-restriction site (R1) sequence followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, which is followed by a loop sequence of defined sequence (X), comprising, for example, about 3 to about 10 nucleotides.

**Figure 7B:** The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence that will result in a siNA transcript having specificity for a SARS target sequence and having self-complementary sense and antisense regions.

**Figure 7C:** The construct is heated (for example to about 95°C) to linearize the sequence, thus allowing extension of a complementary second DNA strand using a primer to the 3'-restriction sequence of the first strand. The double-stranded DNA is then inserted into an appropriate vector for expression in cells. The construct can be designed such that a 3'-terminal nucleotide overhang results from the transcription, for example by engineering restriction sites and/or utilizing a poly-U termination region as described in Paul *et al.*, 2002, *Nature Biotechnology*, 29, 505-508.

**Figure 8A-C** is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate double-stranded siNA constructs.

**Figure 8A:** A DNA oligomer is synthesized with a 5'-restriction (R1) site sequence followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, and which is followed by a 3'-restriction site (R2) which is adjacent to a loop sequence of defined sequence (X).

**Figure 8B:** The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence.

**Figure 8C:** The construct is processed by restriction enzymes specific to R1 and R2 to generate a double-stranded DNA which is then inserted into an appropriate vector for expression in cells. The transcription cassette is designed such that a U6 promoter region flanks each side of the dsDNA which generates the separate sense and antisense

strands of the siNA. Poly T termination sequences can be added to the constructs to generate U overhangs in the resulting transcript.

Figure 9A-E is a diagrammatic representation of a method used to determine target sites for siNA mediated RNAi within a particular target nucleic acid sequence, such as messenger RNA.

Figure 9A: A pool of siNA oligonucleotides are synthesized wherein the antisense region of the siNA constructs has complementarity to target sites across the target nucleic acid sequence, and wherein the sense region comprises sequence complementary to the antisense region of the siNA.

Figure 9B&C: (Figure 9B) The sequences are pooled and are inserted into vectors such that (Figure 9C) transfection of a vector into cells results in the expression of the siNA.

Figure 9D: Cells are sorted based on phenotypic change that is associated with modulation of the target nucleic acid sequence.

Figure 9E: The siNA is isolated from the sorted cells and is sequenced to identify efficacious target sites within the target nucleic acid sequence.

Figure 10 shows non-limiting examples of different stabilization chemistries (1-10) that can be used, for example, to stabilize the 3'-end of siNA sequences of the invention, including (1) [3'-3']-inverted deoxyribose; (2) deoxyribonucleotide; (3) [5'-3']-3'-deoxyribonucleotide; (4) [5'-3']-ribonucleotide; (5) [5'-3']-3'-O-methyl ribonucleotide; (6) 3'-glyceryl; (7) [3'-5']-3'-deoxyribonucleotide; (8) [3'-3']-deoxyribonucleotide; (9) [5'-2']-deoxyribonucleotide; and (10) [5'-3']-dideoxyribonucleotide. In addition to modified and unmodified backbone chemistries indicated in the figure, these chemistries can be combined with different backbone modifications as described herein, for example, backbone modifications having Formula I. In addition, the 2'-deoxy nucleotide shown 5' to the terminal modifications shown can be another modified or unmodified nucleotide or non-nucleotide described herein, for example modifications having any of Formulae I-VII or any combination thereof.

**Figure 11** shows a non-limiting example of a strategy used to identify chemically modified siNA constructs of the invention that are nuclease resistance while preserving the ability to mediate RNAi activity. Chemical modifications are introduced into the siNA construct based on educated design parameters (e.g. introducing 2'-mofications, base modifications, backbone modifications, terminal cap modifications etc). The modified construct is tested in an appropriate system (e.g. human serum for nuclease resistance, shown, or an animal model for PK/delivery parameters). In parallel, the siNA construct is tested for RNAi activity, for example in a cell culture system such as a luciferase reporter assay). Lead siNA constructs are then identified which possess a particular characteristic while maintaining RNAi activity, and can be further modified and assayed once again. This same approach can be used to identify siNA-conjugate molecules with improved pharmacokinetic profiles, delivery, and RNAi activity.

**Figure 12** shows non-limiting examples of phosphorylated siNA molecules of the invention, including linear and duplex constructs and asymmetric derivatives thereof.

**Figure 13** shows non-limiting examples of chemically modified terminal phosphate groups of the invention.

**Figure 14A** shows a non-limiting example of methodology used to design self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are identifed in a target nucleic acid sequence. (i) A palindrome or repeat sequence is identified in a nucleic acid target sequence. (ii) A sequence is designed that is complementary to the target nucleic acid sequence and the palindrome sequence. (iii) An inverse repeat sequence of the non-palindrome/repeat portion of the complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complmentary DFO molecule comprising sequence complementary to the nucleic acid target. (iv) The DFO molecule can self-assemble to form a double stranded oligonucleotide. **Figure 14B** shows a non-limiting representative example of a duplex forming oligonucleotide sequence. **Figure 14C** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence. **Figure 14D** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence followed by interaction with a target nucleic acid sequence resulting in modulation of gene expression.

**Figure 15** shows a non-limiting example of the design of self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are incorporated into the DFO constructs that have sequence complementary to any target nucleic acid sequence of interest. Incorporation of these palidrome/repeat sequences allow the design of DFO constructs that form duplexes in which each strand is capable of mediating modulation of target gene expression, for example by RNAi. First, the target sequence is identified. A complementary sequence is then generated in which nucleotide or non-nucleotide modifications (shown as X or Y) are introduced into the complementary sequence that generate an artificial palidrome (shown as XXXYXXY in the Figure). An inverse repeat of the non-palidrome/repeat complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complimentary DFO comprising sequence complementary to the nucleic acid target. The DFO can self-assemble to form a double stranded oligonucleotide.

**Figure 16** shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 16A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 16B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 17 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. Figure 17A shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. Figure 17B shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in Figure 16.

Figure 18 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifunctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. Figure 18A shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA, and



wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. Figure 18B shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 19 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifunctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. Figure 19A shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. Figure 19B shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a

second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in Figure 18.

Figure 20 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid molecules, such as separate RNA molecules encoding differing proteins, for example, differing viral strains, a virus and a cellular protein involved in viral infection or replication, or differing proteins involved in a common or divergent biologic pathway that is implicated in the maintenance of progression of disease. Each strand of the multifunctional siNA construct comprises a region having complementarity to separate target nucleic acid molecules. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target. These design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

Figure 21 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid sequences within the same target nucleic acid molecule, such as alternate coding regions of a RNA, coding and non-coding regions of a RNA, or alternate splice variant regions of a RNA. Each strand of the multifunctional siNA construct comprises a region having complementarity to the separate regions of the target nucleic acid molecule. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target region. These

design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

## DETAILED DESCRIPTION OF THE INVENTION

### Mechanism of Action of Nucleic Acid Molecules of the Invention

The discussion that follows discusses the proposed mechanism of RNA interference mediated by short interfering RNA as is presently known, and is not meant to be limiting and is not an admission of prior art. Applicant demonstrates herein that chemically-modified short interfering nucleic acids possess similar or improved capacity to mediate RNAi as do siRNA molecules and are expected to possess improved stability and activity *in vivo*; therefore, this discussion is not meant to be limiting only to siRNA and can be applied to siNA as a whole. By "improved capacity to mediate RNAi" or "improved RNAi activity" is meant to include RNAi activity measured *in vitro* and/or *in vivo* where the RNAi activity is a reflection of both the ability of the siNA to mediate RNAi and the stability of the siNAs of the invention. In this invention, the product of these activities can be increased *in vitro* and/or *in vivo* compared to an all RNA siRNA or a siNA containing a plurality of ribonucleotides. In some cases, the activity or stability of the siNA molecule can be decreased (i.e., less than ten-fold), but the overall activity of the siNA molecule is enhanced *in vitro* and/or *in vivo*.

RNA interference refers to the process of sequence specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Fire *et al.*, 1998, *Nature*, 391, 806). The corresponding process in plants is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes which is commonly shared by diverse flora and phyla (Fire *et al.*, 1999,

*Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response though a mechanism that has yet to be fully characterized. This mechanism appears to be different from the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2', 5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L.

10       The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as Dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Berstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from Dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes.

15       Dicer has also been implicated in the excision of 21- and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex containing a siRNA, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded

20       RNA having sequence homologous to the siRNA. Cleavage of the target RNA takes place in the middle of the region complementary to the guide sequence of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). In addition, RNA interference can also involve small RNA (e.g., micro-RNA or miRNA) mediated gene silencing, presumably through cellular mechanisms that regulate chromatin structure and thereby

25       prevent transcription of target gene sequences (see for example Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237). As such, siNA molecules of the invention can be used to mediate gene silencing via interaction with RNA transcripts or alternately by interaction with particular gene sequences, wherein

30       such interaction results in gene silencing either at the transcriptional level or post-transcriptional level.

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mouse embryos. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA.

5 Elbashir *et al.*, 2001, *Nature*, 411, 494, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in *Drosophila* embryonic lysates has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown

10 that 21 nucleotide siRNA duplexes are most active when containing two 2-nucleotide 3'-terminal nucleotide overhangs. Furthermore, substitution of one or both siRNA strands with 2'-deoxy or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of 3'-terminal siRNA nucleotides with deoxy nucleotides was shown to be tolerated. Mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi

15 activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA

20 (Nykanen *et al.*, 2001, *Cell*, 107, 309); however, siRNA molecules lacking a 5'-phosphate are active when introduced exogenously, suggesting that 5'-phosphorylation of siRNA constructs may occur *in vivo*.

#### Synthesis of Nucleic acid Molecules

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using

25 automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small" refers to nucleic acid motifs no more than 100 nucleotides in length, preferably no more than 80 nucleotides in length, and most preferably no more than 50 nucleotides in length; *e.g.*, individual siNA oligonucleotide sequences or siNA sequences synthesized in tandem) are preferably used for exogenous

30 delivery. The simple structure of these molecules increases the ability of the nucleic acid

to invade targeted regions of protein and/or RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

Oligonucleotides (e.g., certain modified oligonucleotides or portions of oligonucleotides lacking ribonucleotides) are synthesized using protocols known in the art, for example as described in Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19, Thompson *et al.*, International PCT Publication No. WO 99/54459, Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684, Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, Brennan *et al.*, 1998, *Biotechnol Bioeng.*, 61, 33-45, and Brennan, U.S. Pat. No. 6,001,311. All of these references are incorporated herein by reference. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2  $\mu\text{mol}$  scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 second coupling step for 2'-deoxy nucleotides or 2'-deoxy-2'-fluoro nucleotides. Table V outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2  $\mu\text{mol}$  scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60  $\mu\text{L}$  of 0.11 M = 6.6  $\mu\text{mol}$ ) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60  $\mu\text{L}$  of 0.25 M = 15  $\mu\text{mol}$ ) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40  $\mu\text{L}$  of 0.11 M = 4.4  $\mu\text{mol}$ ) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40  $\mu\text{L}$  of 0.25 M = 10  $\mu\text{mol}$ ) can be used in each coupling cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM  $\text{I}_2$ , 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained

from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

Deprotection of the DNA-based oligonucleotides is performed as follows: the  
5 polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aqueous methylamine (1 mL) at 65 °C for 10 minutes. After cooling to -20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H<sub>2</sub>O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants,  
10 containing the oligoribonucleotide, are dried to a white powder.

The method of synthesis used for RNA including certain siNA molecules of the invention follows the procedure as described in Usman *et al.*, 1987, *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990, *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, and  
15 makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 µmol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides.  
20 Table V outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 µmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 µL of 0.11 M = 6.6 µmol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 µL of 0.25 M = 15  
25 µmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 µL of 0.11 M = 13.2 µmol) of alkylsilyl (ribo) protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 µL of 0.25 M = 30 µmol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc.  
30 synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems,

- Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM I<sub>2</sub>, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.).
- 5 Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide 0.05 M in acetonitrile) is used.
- 10 Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to -20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of
- 15 EtOH:MeCN:H<sub>2</sub>O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 µL of a solution of 1.5 mL *N*-methylpyrrolidinone, 750 µL TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C.
- 20 After 1.5 h, the oligomer is quenched with 1.5 M NH<sub>4</sub>HCO<sub>3</sub>.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65 °C for 15 minutes. The vial is brought to room temperature TEA•3HF (0.1 mL) is added and the vial is

25 heated at 65 °C for 15 minutes. The sample is cooled at -20 °C and then quenched with 1.5 M NH<sub>4</sub>HCO<sub>3</sub>.

For purification of the trityl-on oligomers, the quenched NH<sub>4</sub>HCO<sub>3</sub> solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA is

30 detritylated with 0.5% TFA for 13 minutes. The cartridge is then washed again with



water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

The average stepwise coupling yields are typically >98% (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that  
5 the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96-well format.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example, by ligation (Moore *et al.*, 1992, *Science* 256, 9923; Draper *et al.*, International PCT publication No.  
10 WO 93/23569; Shabarova *et al.*, 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.*, 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.*, 1997, *Bioconjugate Chem.* 8, 204), or by hybridization following synthesis and/or deprotection.

The siNA molecules of the invention can also be synthesized via a tandem synthesis methodology as described in Example 1 herein, wherein both siNA strands are  
15 synthesized as a single contiguous oligonucleotide fragment or strand separated by a cleavable linker which is subsequently cleaved to provide separate siNA fragments or strands that hybridize and permit purification of the siNA duplex. The linker can be a polynucleotide linker or a non-nucleotide linker. The tandem synthesis of siNA as described herein can be readily adapted to both multiwell/multiplate synthesis platforms  
20 such as 96 well or similarly larger multi-well platforms. The tandem synthesis of siNA as described herein can also be readily adapted to large scale synthesis platforms employing batch reactors, synthesis columns and the like.

A siNA molecule can also be assembled from two distinct nucleic acid strands or fragments wherein one fragment includes the sense region and the second fragment  
25 includes the antisense region of the RNA molecule.

The nucleic acid molecules of the present invention can be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163). siNA constructs can

be purified by gel electrophoresis using general methods or can be purified by high pressure liquid chromatography (HPLC; see Wincott *et al.*, *supra*, the totality of which is hereby incorporated herein by reference) and re-suspended in water.

In another aspect of the invention, siNA molecules of the invention are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules.

Optimizing Activity of the nucleic acid molecule of the invention.

Chemically synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) can prevent their degradation by serum ribonucleases, which can increase their potency (see *e.g.*, Eckstein *et al.*, International Publication No. WO 92/07065; Perrault *et al.*, 1990 *Nature* 344, 565; Pieken *et al.*, 1991, *Science* 253, 314; Usman and Cedergren, 1992, *Trends in Biochem. Sci.* 17, 334; Usman *et al.*, International Publication No. WO 93/15187; and Rossi *et al.*, International Publication No. WO 91/03162; Sproat, U.S. Pat. No. 5,334,711; Gold *et al.*, U.S. Pat. No. 6,300,074; and Burgin *et al.*, *supra*; all of which are incorporated by reference herein). All of the above references describe various chemical modifications that can be made to the base, phosphate and/or sugar moieties of the nucleic acid molecules described herein. Modifications that enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical requirements are desired.

There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-O-allyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992,

TIBS. 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al.*, *International Publication* PCT No. WO 92/07065; Perrault *et al.* *Nature*, 1990, 344, 565-568; Pieken *et al.* *Science*, 1991, 5 253, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, 17, 334-339; Usman *et al.* *International Publication* PCT No. WO 93/15187; Sproat, *U.S. Pat.* No. 5,334,711 and Beigelman *et al.*, 1995, *J. Biol. Chem.*, 270, 25702; Beigelman *et al.*, *International PCT publication* No. WO 97/26270; Beigelman *et al.*, *U.S. Pat.* No. 5,716,824; Usman *et al.*, *U.S. Pat.* No. 5,627,053; Woolf *et al.*, *International PCT* 10 *Publication* No. WO 98/13526; Thompson *et al.*, *USSN* 60/082,404 which was filed on April 20, 1998; Karpeisky *et al.*, 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic Acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina *et al.*, 1997, *Bioorg. Med. Chem.*, 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such 15 publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to 20 promote RNAi in cells is not significantly inhibited.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorodithioate, and/or 5'-methylphosphonate linkages improves stability, excessive modifications can cause some toxicity or decreased activity. Therefore, when designing nucleic acid molecules, the amount of these internucleotide 25 linkages should be minimized. The reduction in the concentration of these linkages should lower toxicity, resulting in increased efficacy and higher specificity of these molecules.

Short interfering nucleic acid (siNA) molecules having chemical modifications that maintain or enhance activity are provided. Such a nucleic acid is also generally more 30 resistant to nucleases than an unmodified nucleic acid. Accordingly, the *in vitro* and/or *in vivo* activity should not be significantly lowered. In cases in which modulation is the

goal, therapeutic nucleic acid molecules delivered exogenously should optimally be stable within cells until translation of the target RNA has been modulated long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Improvements in the chemical synthesis of RNA and DNA (Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677; Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19 (incorporated by reference herein)) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability, as described above.

In one embodiment, nucleic acid molecules of the invention include one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.*, 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in nucleic acid molecules of the invention results in both enhanced affinity and specificity to nucleic acid targets, complementary sequences, or template strands. In another embodiment, nucleic acid molecules of the invention include one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) LNA "locked nucleic acid" nucleotides such as a 2', 4'-C methylene bicyclo nucleotide (see for example Wengel *et al.*, International PCT Publication No. WO 00/66604 and WO 99/14226).

In another embodiment, the invention features conjugates and/or complexes of siNA molecules of the invention. Such conjugates and/or complexes can be used to facilitate delivery of siNA molecules into a biological system, such as a cell. The conjugates and complexes provided by the instant invention can impart therapeutic activity by transferring therapeutic compounds across cellular membranes, altering the pharmacokinetics, and/or modulating the localization of nucleic acid molecules of the invention. The present invention encompasses the design and synthesis of novel conjugates and complexes for the delivery of molecules, including, but not limited to, small molecules, lipids, cholesterol, phospholipids, nucleosides, nucleotides, nucleic

acids, antibodies, toxins, negatively charged polymers and other polymers, for example proteins, peptides, hormones, carbohydrates, polyethylene glycols, or polyamines, across cellular membranes. In general, the transporters described are designed to be used either individually or as part of a multi-component system, with or without degradable linkers.

5 These compounds are expected to improve delivery and/or localization of nucleic acid molecules of the invention into a number of cell types originating from different tissues, in the presence or absence of serum (see Sullenger and Cech, U.S. Pat. No. 5,854,038). Conjugates of the molecules described herein can be attached to biologically active molecules via linkers that are biodegradable, such as biodegradable nucleic acid linker  
10 molecules.

The term "biodegradable linker" as used herein, refers to a nucleic acid or non-nucleic acid linker molecule that is designed as a biodegradable linker to connect one molecule to another molecule, for example, a biologically active molecule to a siNA molecule of the invention or the sense and antisense strands of a siNA molecule of the  
15 invention. The biodegradable linker is designed such that its stability can be modulated for a particular purpose, such as delivery to a particular tissue or cell type. The stability of a nucleic acid-based biodegradable linker molecule can be modulated by using various chemistries, for example combinations of ribonucleotides, deoxyribonucleotides, and chemically-modified nucleotides, such as 2'-O-methyl, 2'-fluoro, 2'-amino, 2'-O-amino,  
20 2'-C-allyl, 2'-O-allyl, and other 2'-modified or base modified nucleotides. The biodegradable nucleic acid linker molecule can be a dimer, trimer, tetramer or longer nucleic acid molecule, for example, an oligonucleotide of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length, or can comprise a single nucleotide with a phosphorus-based linkage, for example, a phosphoramidate or  
25 phosphodiester linkage. The biodegradable nucleic acid linker molecule can also comprise nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications.

The term "biodegradable" as used herein, refers to degradation in a biological system, for example enzymatic degradation or chemical degradation.

The term "biologically active molecule" as used herein, refers to compounds or  
30 molecules that are capable of eliciting or modifying a biological response in a system. Non-limiting examples of biologically active siNA molecules either alone or in

combination with other molecules contemplated by the instant invention include therapeutically active molecules such as antibodies, cholesterol, hormones, antivirals, peptides, proteins, chemotherapeutics, small molecules, vitamins, co-factors, nucleosides, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A chimeras, siNA, dsRNA, allozymes, aptamers, decoys and analogs thereof. Biologically active molecules of the invention also include molecules capable of modulating the pharmacokinetics and/or pharmacodynamics of other biologically active molecules, for example, lipids and polymers such as polyamines, polyamides, polyethylene glycol and other polyethers.

10       The term "phospholipid" as used herein, refers to a hydrophobic molecule comprising at least one phosphorus group. For example, a phospholipid can comprise a phosphorus-containing group and saturated or unsaturated alkyl group, optionally substituted with OH, COOH, oxo, amine, or substituted or unsubstituted aryl groups.

Therapeutic nucleic acid molecules (e.g., siNA molecules) delivered exogenously optimally are stable within cells until reverse transcription of the RNA has been modulated long enough to reduce the levels of the RNA transcript. The nucleic acid molecules are resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

In yet another embodiment, siNA molecules having chemical modifications that maintain or enhance enzymatic activity of proteins involved in RNAi are provided. Such nucleic acids are also generally more resistant to nucleases than unmodified nucleic acids. Thus, *in vitro* and/or *in vivo* the activity should not be significantly lowered.

Use of the nucleic acid-based molecules of the invention will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple siNA molecules targeted to different genes; nucleic acid molecules coupled with known small molecule modulators; or intermittent treatment with combinations of molecules, including different motifs and/or other chemical or

biological molecules). The treatment of subjects with siNA molecules can also include combinations of different types of nucleic acid molecules, such as enzymatic nucleic acid molecules (ribozymes), allozymes, antisense, 2,5-A oligoadenylate, decoys, and aptamers.

- 5 In another aspect a siNA molecule of the invention comprises one or more 5' and/or a 3'- cap structure, for example on only the sense siNA strand, the antisense siNA strand, or both siNA strands.

By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see, for example, Adamic *et al.*, U.S. Pat. No. 10 5,998,203, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and may help in delivery and/or localization within a cell. The cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminal (3'-cap) or may be present on both termini. In non-limiting examples, the 5'-cap includes, but is not limited to, glyceryl, inverted deoxy abasic residue (moiety); 4',5'-methylene nucleotide; 1-(beta-D-erythrofuransyl) nucleotide, 4'-thio nucleotide; 15 carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuransyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 20 moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety.

Non-limiting examples of the 3'-cap include, but are not limited to, glyceryl, 25 inverted deoxy abasic residue (moiety), 4', 5'-methylene nucleotide; 1-(beta-D-erythrofuransyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate; 3-aminopropyl phosphate; 6-aminoethyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; 30 phosphorodithioate; *threo*-pentofuransyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide

moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 5 1993, *Tetrahedron* 49, 1925; incorporated by reference herein).

By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not 10 contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine and therefore lacks a base at the 1'-position.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 15 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO<sub>2</sub> or N(CH<sub>3</sub>)<sub>2</sub>, amino, or SH. The term also includes alkenyl groups that are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. 20 More preferably, it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO<sub>2</sub>, halogen, N(CH<sub>3</sub>)<sub>2</sub>, amino, or SH. The term "alkyl" also includes alkynyl groups that have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, 25 including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably, it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO<sub>2</sub> or N(CH<sub>3</sub>)<sub>2</sub>, amino or SH.



Such alkyl groups can also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group that has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" as used herein is as recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see, for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra*, all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, *Nucleic Acids Res.* 22, 2183. Some of the non-limiting examples of base modifications that can be introduced into nucleic acid molecules include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*, ribothymidine), 5-halouridine (*e.g.*, 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (*e.g.* 6-methyluridine), propyne, and others (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090;

Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents.

In one embodiment, the invention features modified siNA molecules, with phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, phosphotriester, morpholino, amidate, carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications, see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties*, in *Modern Synthetic Methods*, VCH, 331-417, and Mesmaeker *et al.*, 1994, *Novel Backbone Replacements for Oligonucleotides*, in *Carbohydrate Modifications in Antisense Research*, ACS, 24-39.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, see for example Adamic *et al.*, U.S. Pat. No. 5,998,203.

By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, or uracil joined to the 1' carbon of  $\beta$ -D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate. Non-limiting examples of modified nucleotides are shown by Formulae I-VII and/or other modifications described herein.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH<sub>2</sub> or 2'-O-NH<sub>2</sub>, which can be modified or unmodified. Such modified groups are described, for example, in Eckstein *et al.*, U.S. Pat. No. 5,672,695 and Matulic-Adamic *et al.*, U.S. Pat. No. 6,248,878, which are both incorporated by reference in their entireties.

Various modifications to nucleic acid siNA structure can be made to enhance the utility of these molecules. Such modifications will enhance shelf-life, half-life *in vitro*, stability, and ease of introduction of such oligonucleotides to the target site, *e.g.*, to

enhance penetration of cellular membranes, and confer the ability to recognize and bind to targeted cells.

#### Administration of Nucleic Acid Molecules

A siRNA molecule of the invention can be adapted for use to treat for example SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue, alone or in combination with other therapies. For example, a siNA molecule can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in pharmaceutically acceptable formulations. Methods for the delivery of nucleic acid molecules are described in Akhtar *et al.*, 1992, *Trends Cell Bio.*, 2, 139; *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995, Maurer *et al.*, 1999, *Mol. Membr. Biol.*, 16, 129-140; Hofland and Huang, 1999, *Handb. Exp. Pharmacol.*, 137, 165-192; and Lee *et al.*, 2000, *ACS Symp. Ser.*, 752, 184-192, all of which are incorporated herein by reference. Beigelman *et al.*, U.S. Pat. No. 6,395,713 and Sullivan *et al.*, PCT WO 94/02595 further describe the general methods for delivery of nucleic acid molecules. These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a variety of methods known to those of skill in the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as biodegradable polymers, hydrogels, cyclodextrins (see for example Gonzalez *et al.*, 1999, *Bioconjugate Chem.*, 10, 1068-1074; Wang *et al.*, International PCT publication Nos. WO 03/47518 and WO 03/46185), poly(lactic-co-glycolic)acid (PLGA) and PLCA microspheres (see for example US Patent 6,447,796 and US Patent Application Publication No. US 2002130430), biodegradable nanocapsules, and bioadhesive microspheres, or by proteinaceous vectors (O'Hare and Normand, International PCT Publication No. WO 00/53722). In another embodiment, the nucleic acid molecules of the invention can also be formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine-polyethyleneglycol-N-acetylgalactosamine (PEI-PEG-GAL) or polyethyleneimine-polyethyleneglycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives.

Alternatively, the nucleic acid/vehicle combination is locally delivered by direct injection or by use of an infusion pump.

In one embodiment, the nucleic acid molecules or the invention are administered via pulmonary delivery, such as by inhalation of an aerosol or spray dried formulation administered by an inhalation device or nebulizer, providing rapid local uptake of the nucleic acid molecules into relevant pulmonary tissues. Solid particulate compositions containing respirable dry particles of micronized nucleic acid compositions can be prepared by grinding dried or lyophilized nucleic acid compositions, and then passing the micronized composition through, for example, a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprising the nucleic acid compositions of the invention can optionally contain a dispersant which serves to facilitate the formation of an aerosol as well as other therapeutic compounds. A suitable dispersant is lactose, which can be blended with the nucleic acid compound in any suitable ratio, such as a 1 to 1 ratio by weight.

Aerosols of liquid particles comprising a nucleic acid composition of the invention can be produced by any suitable means, such as with a nebulizer (see for example US 4,501,729). Nebulizers are commercially available devices which transform solutions or suspensions of an active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers comprise the active ingredient in a liquid carrier in an amount of up to 40% w/w preferably less than 20% w/w of the formulation. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride or other suitable salts. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, anti-oxidants, flavorings, volatile oils, buffering agents and emulsifiers and other formulation surfactants. The aerosols of solid particles comprising the active composition and surfactant can likewise be produced with any solid particulate aerosol generator. Aerosol generators for administering solid particulate therapeutics to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a therapeutic composition at a rate

suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which can be delivered by means of an insufflator. In the insufflator, the powder, e.g., a metered dose thereof effective to carry out the

5 treatments described herein, is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as

10 lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted

15 to deliver a metered volume to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation can additionally contain one or more co-solvents, for example, ethanol, emulsifiers and other formulation surfactants, such as oleic acid or

20 sorbitan trioleate, anti-oxidants and suitable flavoring agents. Other methods for pulmonary delivery are described in, for example US Patent Application No. 20040037780, and US Patent Nos. 6,592,904; 6,582,728; 6,565,885.

In one embodiment, a siNA molecule of the invention is complexed with membrane disruptive agents such as those described in U.S. Patent Application

25 Publication No. 20010007666, incorporated by reference herein in its entirety including the drawings. In another embodiment, the membrane disruptive agent or agents and the siNA molecule are also complexed with a cationic lipid or helper lipid molecule, such as those lipids described in U.S. Patent No. 6,235,310, incorporated by reference herein in its entirety including the drawings.

30 Thus, the invention features a pharmaceutical composition comprising one or more nucleic acid(s) of the invention in an acceptable carrier, such as a stabilizer, buffer, and

the like. The polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced into a subject by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions, suspensions for injectable administration, and the other compositions known in the art.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or subject, including for example a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (*i.e.*, a cell to which the negatively charged nucleic acid is desirable for delivery). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms that prevent the composition or formulation from exerting its effect.

By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes that lead to systemic absorption include, without limitation: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes exposes the siNA molecules of the invention to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation that can facilitate the

association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as cells producing excess repeat expansion genes.

5 By "pharmaceutically acceptable formulation" is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: P-glycoprotein inhibitors (such as Pluronic P85),;  
10 biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery (Emerich, DF *et al*, 1999, *Cell Transplant*, 8, 47-58); and loaded nanoparticles, such as those made of polybutylcyanoacrylate. Other non-limiting examples of delivery strategies for the nucleic acid molecules of the instant invention include material described in Boado *et al.*, 1998, *J. Pharm. Sci.*, 87, 1308-1315; Tyler *et al.*, 1999, *FEBS Lett.*, 421, 280-284; Pardridge *et al.*, 1995, *PNAS USA.*, 92, 5592-5596;  
15 Boado, 1995, *Adv. Drug Delivery Rev.*, 15, 73-107; Aldrian-Herrada *et al.*, 1998, *Nucleic Acids Res.*, 26, 4910-4916; and Tyler *et al.*, 1999, *PNAS USA.*, 96, 7053-7058.

The invention also features the use of the composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes). These formulations offer a method for  
20 increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al. Chem. Rev.* 1995, 95, 2601-2627; Ishiwata *et al.*, *Chem. Pharm. Bull.* 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al.*, *Science* 1995, 267, 1275-1276; Oku *et al.*, 1995, *Biochim. Biophys. Acta*, 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to  
25 conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al.*, *J. Biol. Chem.* 1995, 42, 24864-24870; Choi *et al.*, International PCT  
30

Publication No. WO 96/10391; Ansell *et al.*, International PCT Publication No. WO 96/10390; Holland *et al.*, International PCT Publication No. WO 96/10392). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid  
5 accumulation in metabolically aggressive MPS tissues such as the liver and spleen.

The present invention also includes compositions prepared for storage or administration that include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described,  
10 for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985), hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

15 A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent  
20 medication, and other factors that those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray, or rectally in dosage  
25 unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a  
30 pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically



acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard  
5 or soft capsules, or syrups or elixirs.

Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable  
10 preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be, for example, inert diluents; such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for  
15 example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl  
20 monostearate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

25 Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example,  
30 lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain

aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a

demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above.

5 The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any

10 bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The nucleic acid molecules of the invention can also be administered in the form of suppositories, *e.g.*, for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at

15 ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either

20 be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per subject per day). The amount of active ingredient that can be

25 combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

It is understood that the specific dose level for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age,

30 body weight, general health, sex, diet, time of administration, route of administration,

and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

The nucleic acid molecules of the present invention can also be administered to a subject in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

In one embodiment, the invention comprises compositions suitable for administering nucleic acid molecules of the invention to specific cell types. For example, the asialoglycoprotein receptor (ASGPr) (Wu and Wu, 1987, *J. Biol. Chem.* 262, 4429-4432) is unique to hepatocytes and binds branched galactose-terminal glycoproteins, such as asialoorosomucoid (ASOR). In another example, the folate receptor is overexpressed in many cancer cells. Binding of such glycoproteins, synthetic glycoconjugates, or folates to the receptor takes place with an affinity that strongly depends on the degree of branching of the oligosaccharide chain, for example, triantennary structures are bound with greater affinity than biantennary or monoantennary chains (Baenziger and Fiete, 1980, *Cell*, 22, 611-620; Connolly *et al.*, 1982, *J. Biol. Chem.*, 257, 939-945). Lee and Lee, 1987, *Glycoconjugate J.*, 4, 317-328, obtained this high specificity through the use of N-acetyl-D-galactosamine as the carbohydrate moiety, which has higher affinity for the receptor, compared to galactose. This "clustering effect" has also been described for the binding and uptake of mannosyl-terminating glycoproteins or glycoconjugates (Ponpipom *et al.*, 1981, *J. Med. Chem.*, 24, 1388-1395). The use of galactose, galactosamine, or folate based conjugates to transport exogenous compounds across cell membranes can provide a targeted delivery approach to, for example, the treatment of liver disease, cancers of the liver, or other cancers. The use of bioconjugates can also provide a reduction in the required dose of therapeutic compounds required for treatment. Furthermore, therapeutic bioavailability,

pharmacodynamics, and pharmacokinetic parameters can be modulated through the use of nucleic acid bioconjugates of the invention. Non-limiting examples of such bioconjugates are described in Vargeese *et al.*, USSN 10/201,394, filed August 13, 2001; and Matulic-Adamic *et al.*, USSN 10/151,116, filed May 17, 2002. In one embodiment, 5 nucleic acid molecules of the invention are complexed with or covalently attached to nanoparticles, such as Hepatitis B virus S, M, or L envelope proteins (see for example Yamado *et al.*, 2003, *Nature Biotechnology*, 21, 885). In one embodiment, nucleic acid molecules of the invention are delivered with specificity for human tumor cells, specifically non-apoptotic human tumor cells including for example T-cells, hepatocytes, 10 breast carcinoma cells, ovarian carcinoma cells, melanoma cells, intestinal epithelial cells, prostate cells, testicular cells, non-small cell lung cancers, small cell lung cancers, etc.

Alternatively, certain siNA molecules of the instant invention can be expressed within cells from eukaryotic promoters (*e.g.*, Izant and Weintraub, 1985, *Science*, 229, 15 345; McGarry and Lindquist, 1986, *Proc. Natl. Acad. Sci.*, USA 83, 399; Scanlon *et al.*, 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Dropulic *et al.*, 1992, *J. Virol.*, 66, 1432-41; Weerasinghe *et al.*, 1991, *J. Virol.*, 65, 5531-4; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. USA*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Sarver *et al.*, 1990 *Science*, 247, 20 1222-1225; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Good *et al.*, 1997, *Gene Therapy*, 4, 45. Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 25 94/02595; Ohkawa *et al.*, 1992, *Nucleic Acids Symp. Ser.*, 27, 15-6; Taira *et al.*, 1991, *Nucleic Acids Res.*, 19, 5125-30; Ventura *et al.*, 1993, *Nucleic Acids Res.*, 21, 3249-55; Chowrira *et al.*, 1994, *J. Biol. Chem.*, 269, 25856.

In another aspect of the invention, RNA molecules of the present invention can be expressed from transcription units (see for example Couture *et al.*, 1996, *TIG.*, 12, 510) 30 inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited

to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. In another embodiment, pol III based constructs are used to express nucleic acid molecules of the invention (see for example Thompson, U.S. Pats. Nos. 5,902,880 and 6,146,886). The recombinant vectors capable of expressing the siNA molecules can be delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecule interacts with the target mRNA and generates an RNAi response. Delivery of siNA molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.*, 1996, *TIG.*, 12, 510).

In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the instant invention. The expression vector can encode one or both strands of a siNA duplex, or a single self-complementary strand that self hybridizes into a siNA duplex. The nucleic acid sequences encoding the siNA molecules of the instant invention can be operably linked in a manner that allows expression of the siNA molecule (see for example Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online publication doi:10.1038/nm725).

In another aspect, the invention features an expression vector comprising: a) a transcription initiation region (*e.g.*, eukaryotic pol I, II or III initiation region); b) a transcription termination region (*e.g.*, eukaryotic pol I, II or III termination region); and c) a nucleic acid sequence encoding at least one of the siNA molecules of the instant invention, wherein said sequence is operably linked to said initiation region and said termination region in a manner that allows expression and/or delivery of the siNA molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the siNA of the invention; and/or an intron (intervening sequences).

Transcription of the siNA molecule sequences can be driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.*, 21, 2867-72; Lieber *et al.*, 1993, *Methods Enzymol.*, 217, 47-66; Zhou *et al.*, 1990, *Mol. Cell. Biol.*, 10, 4529-37). Several investigators have demonstrated that nucleic acid molecules expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Yu *et al.*, 1993, *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier *et al.*, 1992, *EMBO J.*, 11, 4411-8; Lisiewicz *et al.*, 1993, *Proc. Natl. Acad. Sci. U. S. A*, 90, 8000-4; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Sullenger & Cech, 1993, *Science*, 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as siNA in cells (Thompson *et al.*, *supra*; Couture and Stinchcomb, 1996, *supra*; Noonberg *et al.*, 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg *et al.*, U.S. Pat. No. 5,624,803; Good *et al.*, 1997, *Gene Ther.*, 4, 45; Beigelman *et al.*, International PCT Publication No. WO 96/18736. The above siNA transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, 1996, *supra*).

In another aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the siNA molecules of the invention in a manner that allows expression of that siNA molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; and c) a nucleic acid sequence encoding at least one strand of the siNA molecule,

wherein the sequence is operably linked to the initiation region and the termination region in a manner that allows expression and/or delivery of the siNA molecule.

In another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; and d) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the open reading frame and the termination region in a manner that allows expression and/or delivery of the siNA molecule. In yet another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; and d) a nucleic acid sequence encoding at least one siNA molecule, wherein the sequence is operably linked to the initiation region, the intron and the termination region in a manner which allows expression and/or delivery of the nucleic acid molecule.

In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; and e) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the intron, the open reading frame and the termination region in a manner which allows expression and/or delivery of the siNA molecule.

#### SARS virus biology and biochemistry

The following discussion is adapted from the report, "Preliminary Clinical Description of Severe Acute Respiratory Syndrome", World Health Organization, Geneva, Switzerland, available at the Centers for Disease Control and Prevention website.

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a coronavirus, called SARS-associated coronavirus (SARS-CoV). SARS was first reported in Asia in February 2003. Over the next few months, the illness spread to more than two dozen countries in North America, South America, Europe, and Asia before the SARS



global outbreak of 2003 was contained. According to the World Health Organization (WHO), a total of 8,098 people worldwide became sick with SARS during the 2003 outbreak. Of these, 774 died.

The incubation period for SARS is typically 2--7 days; however, isolated reports  
5 have suggested an incubation period as long as 10 days. The illness begins generally with a prodrome of fever ( $>100.4^{\circ}\text{F}$  [ $>38.0^{\circ}\text{C}$ ]). Fever often is high, sometimes is associated with chills and rigors, and might be accompanied by other symptoms, including headache, malaise, and myalgia. At the onset of illness, some persons have mild respiratory symptoms. Typically, rash and neurologic or gastrointestinal findings are  
10 absent; however, some patients have reported diarrhea during the febrile prodrome.

After 3--7 days, a lower respiratory phase begins with the onset of a dry, nonproductive cough or dyspnea, which might be accompanied by or progress to hypoxemia. In 10%--20% of cases, the respiratory illness is severe enough to require intubation and mechanical ventilation. Death may result from progressive respiratory  
15 failure due to alveolar damage. The case-fatality rate among persons with illness meeting the current WHO case definition of SARS is approximately 3%.

Chest radiographs might be normal during the febrile prodrome and throughout the course of illness. However, in a substantial proportion of patients, the respiratory phase is characterized by early focal interstitial infiltrates progressing to more generalized,  
20 patchy, interstitial infiltrates. Some chest radiographs from patients in the late stages of SARS also have shown areas of consolidation.

Early in the course of disease, the absolute lymphocyte count is often decreased. Overall white blood cell counts have generally been normal or decreased. At the peak of the respiratory illness, approximately 50% of patients have leukopenia and  
25 thrombocytopenia or low-normal platelet counts (50,000--150,000/ $\mu\text{L}$ ). Early in the respiratory phase, elevated creatine phosphokinase levels (as high as 3,000 IU/L) and hepatic transaminases (two to six times the upper limits of normal) have been noted. In the majority of patients, renal function has remained normal.

The severity of illness might be highly variable, ranging from mild illness to death. Although a few close contacts of patients with SARS have developed a similar illness, the majority have remained well. Some close contacts have reported a mild, febrile illness without respiratory signs or symptoms, suggesting the illness might not always progress to the respiratory phase.

Treatment regimens have included several antibiotics to presumptively treat known bacterial agents of atypical pneumonia. In several locations, therapy also has included antiviral agents such as oseltamivir or ribavirin. Steroids have also been administered orally or intravenously to patients in combination with ribavirin and other antimicrobials. At present, the most efficacious treatment regimen, if any, is unknown.

The causative agent of SARS appears to be a novel coronavirus that was isolated from patients who met the case definition of SARS (see Ksiazek et al., 2003, New England Journal of Medicine, 10.1056/NEJMoa030781. Indirect fluorescent antibody tests and enzyme-linked immunosorbent assays made with the new coronavirus isolate have been used to demonstrate a virus-specific serologic response. Amplification of short regions of the polymerase gene, (the most strongly conserved part of the Coronavirus genome) by reverse transcriptase polymerase chain reaction (RT-PCR) and nucleotide sequencing revealed that the SARS virus is a novel Coronavirus which has not previously been present in human populations. This conclusion is confirmed by serological (antigenic) investigations. The sequence of the SARS associated coronavirus was recently made available through the CDC.

Viral entry into cells occurs via endocytosis and membrane fusion. Replication occurs in the cytoplasm. Initially, the 5' 20kb of the (+)sense genome is translated to produce a viral polymerase, which then produces a full-length (-)sense strand. This is used as a template to produce mRNA as a nested set of transcripts, all with an identical 5' non-translated leader sequence of 72nt and coincident 3' polyadenylated ends. Each mRNA is monocistronic, the genes at the 5' end being translated from the longest mRNA. These unusual cytoplasmic structures are produced not by splicing but by the polymerase during transcription. Between each of the genes there is a repeated intergenic sequence - UCUAAAC - which interacts with the transcriptase plus cellular factors to splice the leader sequence onto the start of each ORF. Viral assembly occurs by budding

into the golgi apparatus, and viral particles are transported to the surface of the cell and are subsequently released.

The SARS virus can be grown in Vero cells (a fibroblast cell line isolated in 1962 from a primate). This is a novel property for human coronaviruses which usually cannot be cultivated. In these cells, virus infection results in a cytopathic effect, and budding of  
5 Coronavirus-like particles from the endoplasmic reticulum within infected cells.

Detection of the SARS virus can be accomplished with serological testing and molecular diagnostic procedures. Serological testing for anti-Coronavirus antibodies consists of indirect fluorescent antibody testing and enzyme-linked immunosorbent  
10 assays (ELISA) which detect antibodies against the virus produced in response to infection. Molecular testing consists of reverse transcriptase-polymerase chain reaction (RT-PCR) tests specific for the RNA from the novel Coronavirus.

The use of small interfering nucleic acid molecules targeting SARS genes therefore provides a class of novel therapeutic agents that can be used in the treatment and  
15 diagnosis of SARS virus infection, acute respiratory failure, viral pneumonia, or any other disease or condition that responds to modulation of SARS genes.

Examples:

The following are non-limiting examples showing the selection, isolation, synthesis and activity of nucleic acids of the instant invention.

20 Example 1: Tandem synthesis of siNA constructs

Exemplary siNA molecules of the invention are synthesized in tandem using a cleavable linker, for example, a succinyl-based linker. Tandem synthesis as described herein is followed by a one-step purification process that provides RNAi molecules in high yield. This approach is highly amenable to siNA synthesis in support of high  
25 throughput RNAi screening, and can be readily adapted to multi-column or multi-well synthesis platforms.

After completing a tandem synthesis of a siNA oligo and its complement in which the 5'-terminal dimethoxytrityl (5'-ODMT) group remains intact (trityl on synthesis), the

oligonucleotides are deprotected as described above. Following deprotection, the siNA sequence strands are allowed to spontaneously hybridize. This hybridization yields a duplex in which one strand has retained the 5'-O-DMT group while the complementary strand comprises a terminal 5'-hydroxyl. The newly formed duplex behaves as a single molecule during routine solid-phase extraction purification (Trityl-On purification) even though only one molecule has a dimethoxytrityl group. Because the strands form a stable duplex, this dimethoxytrityl group (or an equivalent group, such as other trityl groups or other hydrophobic moieties) is all that is required to purify the pair of oligos, for example, by using a C18 cartridge.

Standard phosphoramidite synthesis chemistry is used up to the point of introducing a tandem linker, such as an inverted deoxy abasic succinate or glyceryl succinate linker (see Figure 1) or an equivalent cleavable linker. A non-limiting example of linker coupling conditions that can be used includes a hindered base such as diisopropylethylamine (DIPA) and/or DMAP in the presence of an activator reagent such as Bromotripyrrolidinophosphoniumhexafluorophosphate (PyBrOP). After the linker is coupled, standard synthesis chemistry is utilized to complete synthesis of the second sequence leaving the terminal the 5'-O-DMT intact. Following synthesis, the resulting oligonucleotide is deprotected according to the procedures described herein and quenched with a suitable buffer, for example with 50mM NaOAc or 1.5M  $\text{NH}_4\text{H}_2\text{CO}_3$ .

Purification of the siNA duplex can be readily accomplished using solid phase extraction, for example using a Waters C18 SepPak 1g cartridge conditioned with 1 column volume (CV) of acetonitrile, 2 CV  $\text{H}_2\text{O}$ , and 2 CV 50mM NaOAc. The sample is loaded and then washed with 1 CV  $\text{H}_2\text{O}$  or 50mM NaOAc. Failure sequences are eluted with 1 CV 14% ACN (Aqueous with 50mM NaOAc and 50mM NaCl). The column is then washed, for example with 1 CV  $\text{H}_2\text{O}$  followed by on-column detritylation, for example by passing 1 CV of 1% aqueous trifluoroacetic acid (TFA) over the column, then adding a second CV of 1% aqueous TFA to the column and allowing to stand for approximately 10 minutes. The remaining TFA solution is removed and the column washed with  $\text{H}_2\text{O}$  followed by 1 CV 1M NaCl and additional  $\text{H}_2\text{O}$ . The siNA duplex product is then eluted, for example, using 1 CV 20% aqueous CAN.

Figure 2 provides an example of MALDI-TOF mass spectrometry analysis of a purified siNA construct in which each peak corresponds to the calculated mass of an individual siNA strand of the siNA duplex. The same purified siNA provides three peaks when analyzed by capillary gel electrophoresis (CGE), one peak presumably corresponding to the duplex siNA, and two peaks presumably corresponding to the separate siNA sequence strands. Ion exchange HPLC analysis of the same siNA construct only shows a single peak. Testing of the purified siNA construct using a luciferase reporter assay described below demonstrated the same RNAi activity compared to siNA constructs generated from separately synthesized oligonucleotide sequence strands.

10 Example 2: Identification of potential siNA target sites in any RNA sequence

The sequence of an RNA target of interest, such as a viral or human mRNA transcript, is screened for target sites, for example by using a computer folding algorithm. In a non-limiting example, the sequence of a gene or RNA gene transcript derived from a database, such as Genbank, is used to generate siNA targets having complementarity to the target. Such sequences can be obtained from a database, or can be determined experimentally as known in the art. Target sites that are known, for example, those target sites determined to be effective target sites based on studies with other nucleic acid molecules, for example ribozymes or antisense, or those targets known to be associated with a disease or condition such as those sites containing mutations or deletions, can be used to design siNA molecules targeting those sites. Various parameters can be used to determine which sites are the most suitable target sites within the target RNA sequence. These parameters include but are not limited to secondary or tertiary RNA structure, the nucleotide base composition of the target sequence, the degree of homology between various regions of the target sequence, or the relative position of the target sequence within the RNA transcript. Based on these determinations, any number of target sites within the RNA transcript can be chosen to screen siNA molecules for efficacy, for example by using *in vitro* RNA cleavage assays, cell culture, or animal models. In a non-limiting example, anywhere from 1 to 1000 target sites are chosen within the transcript based on the size of the siNA construct to be used. High throughput screening assays can be developed for screening siNA molecules

using methods known in the art, such as with multi-well or multi-plate assays to determine efficient reduction in target gene expression.

Example 3: Selection of siNA molecule target sites in a RNA

The following non-limiting steps can be used to carry out the selection of siNAs targeting a given gene sequence or transcript.

1. The target sequence is parsed *in silico* into a list of all fragments or subsequences of a particular length, for example 23 nucleotide fragments, contained within the target sequence. This step is typically carried out using a custom Perl script, but commercial sequence analysis programs such as Oligo, MacVector, or the GCG Wisconsin Package can be employed as well.
2. In some instances the siNAs correspond to more than one target sequence; such would be the case for example in targeting different transcripts of the same gene, targeting different transcripts of more than one gene, or for targeting both the human gene and an animal homolog. In this case, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find matching sequences in each list. The subsequences are then ranked according to the number of target sequences that contain the given subsequence; the goal is to find subsequences that are present in most or all of the target sequences. Alternately, the ranking can identify subsequences that are unique to a target sequence, such as a mutant target sequence. Such an approach would enable the use of siNA to target specifically the mutant sequence and not effect the expression of the normal sequence.
3. In some instances the siNA subsequences are absent in one or more sequences while present in the desired target sequence; such would be the case if the siNA targets a gene with a paralogous family member that is to remain untargeted. As in case 2 above, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find sequences that are present in the target gene but are absent in the untargeted paralog.

4. The ranked siNA subsequences can be further analyzed and ranked according to GC content. A preference can be given to sites containing 30-70% GC, with a further preference to sites containing 40-60% GC.
5. The ranked siNA subsequences can be further analyzed and ranked according to self-folding and internal hairpins. Weaker internal folds are preferred; strong hairpin structures are to be avoided.
6. The ranked siNA subsequences can be further analyzed and ranked according to whether they have runs of GGG or CCC in the sequence. GGG (or even more Gs) in either strand can make oligonucleotide synthesis problematic and can potentially interfere with RNAi activity, so it is avoided whenever better sequences are available. CCC is searched in the target strand because that will place GGG in the antisense strand.
7. The ranked siNA subsequences can be further analyzed and ranked according to whether they have the dinucleotide UU (uridine dinucleotide) on the 3'-end of the sequence, and/or AA on the 5'-end of the sequence (to yield 3' UU on the antisense sequence). These sequences allow one to design siNA molecules with terminal TT thymidine dinucleotides.
8. Four or five target sites are chosen from the ranked list of subsequences as described above. For example, in subsequences having 23 nucleotides, the right 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the upper (sense) strand of the siNA duplex, while the reverse complement of the left 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the lower (antisense) strand of the siNA duplex (see Tables II and III). If terminal TT residues are desired for the sequence (as described in paragraph 7), then the two 3' terminal nucleotides of both the sense and antisense strands are replaced by TT prior to synthesizing the oligos.
9. The siNA molecules are screened in an *in vitro*, cell culture or animal model system to identify the most active siNA molecule or the most preferred target site within the target RNA sequence.

10. Other design considerations can be used when selecting target nucleic acid sequences, see for example Reynolds *et al.*, 2004, *Nature Biotechnology Advanced Online Publication*, 1 February 2004, doi:10.1038/nbt936 and Ui-Tei *et al.*, 2004, *Nucleic Acids Research*, 32, doi:10.1093/nar/gkh247.

5 In an alternate approach, a pool of siNA constructs specific to a SARS target sequence is used to screen for target sites in cells expressing SARS RNA, such as VERO cells and/or FRhk-4 cells. The general strategy used in this approach is shown in Figure 9. A non-limiting example of such is a pool comprising sequences having SEQ ID NOs: 1-3392. Cells expressing SARS (e.g., VERO cells and/or FRhk-4 cells) are transfected  
10 with the pool of siNA constructs and cells that demonstrate a phenotype associated with SARS inhibition are sorted. The pool of siNA constructs can be expressed from transcription cassettes inserted into appropriate vectors (see for example Figure 7 and Figure 8). The siNA from cells demonstrating a positive phenotypic change (e.g., decreased proliferation, decreased SARS mRNA levels or decreased SARS protein  
15 expression), are sequenced to determine the most suitable target site(s) within the target SARS RNA sequence.

#### Example 4: SARS targeted siNA design

siNA target sites were chosen by analyzing sequences of the SARS RNA target and optionally prioritizing the target sites on the basis of folding (structure of any given  
20 sequence analyzed to determine siNA accessibility to the target), by using a library of siNA molecules as described in Example 3, or alternately by using an *in vitro* siNA system as described in Example 6 herein. siNA molecules were designed that could bind each target and are optionally individually analyzed by computer folding to assess whether the siNA molecule can interact with the target sequence. Varying the length of  
25 the siNA molecules can be chosen to optimize activity. Generally, a sufficient number of complementary nucleotide bases are chosen to bind to, or otherwise interact with, the target RNA, but the degree of complementarity can be modulated to accommodate siNA duplexes or varying length or base composition. By using such methodologies, siNA molecules can be designed to target sites within any known RNA sequence, for example  
30 those RNA sequences corresponding to the any gene transcript.



Chemically modified siNA constructs are designed to provide nuclease stability for systemic administration in vivo and/or improved pharmacokinetic, localization, and delivery properties while preserving the ability to mediate RNAi activity. Chemical modifications as described herein are introduced synthetically using synthetic methods described herein and those generally known in the art. The synthetic siNA constructs are then assayed for nuclease stability in serum and/or cellular/tissue extracts (e.g. liver extracts). The synthetic siNA constructs are also tested in parallel for RNAi activity using an appropriate assay, such as a luciferase reporter assay as described herein or another suitable assay that can quantify RNAi activity. Synthetic siNA constructs that possess both nuclease stability and RNAi activity can be further modified and re-evaluated in stability and activity assays. The chemical modifications of the stabilized active siNA constructs can then be applied to any siNA sequence targeting any chosen RNA and used, for example, in target screening assays to pick lead siNA compounds for therapeutic development (see for example Figure 11).

15 Example 5: Chemical Synthesis and Purification of siNA

siNA molecules can be designed to interact with various sites in the RNA message, for example, target sequences within the RNA sequences described herein. The sequence of one strand of the siNA molecule(s) is complementary to the target site sequences described above. The siNA molecules can be chemically synthesized using methods described herein. Inactive siNA molecules that are used as control sequences can be synthesized by scrambling the sequence of the siNA molecules such that it is not complementary to the target sequence. Generally, siNA constructs can be synthesized using solid phase oligonucleotide synthesis methods as described herein (see for example Usman *et al.*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,117,657; 6,353,098; 20 6,362,323; 6,437,117; 6,469,158; Scaringe *et al.*, US Patent Nos. 6,111,086; 6,008,400; 25 6,111,086 all incorporated by reference herein in their entirety).

In a non-limiting example, RNA oligonucleotides are synthesized in a stepwise fashion using the phosphoramidite chemistry as is known in the art. Standard phosphoramidite chemistry involves the use of nucleosides comprising any of 5'-O-dimethoxytrityl, 2'-O-tert-butyldimethylsilyl, 3'-O-2-Cyanoethyl N,N-diisopropylphosphoroamidite groups, and exocyclic amine protecting groups (e.g. N6-benzoyl adenosine,

N4 acetyl cytidine, and N2-isobutyryl guanosine). Alternately, 2'-O-Silyl Ethers can be used in conjunction with acid-labile 2'-O-orthoester protecting groups in the synthesis of RNA as described by Scaringe *supra*. Differing 2' chemistries can require different protecting groups, for example 2'-deoxy-2'-amino nucleosides can utilize N-phthaloyl protection as described by Usman *et al.*, US Patent 5,631,360, incorporated by reference  
5 herein in its entirety).

During solid phase synthesis, each nucleotide is added sequentially (3'- to 5'- direction) to the solid support-bound oligonucleotide. The first nucleoside at the 3'-end of the chain is covalently attached to a solid support (e.g., controlled pore glass or polystyrene) using various linkers. The nucleotide precursor, a ribonucleoside  
10 phosphoramidite, and activator are combined resulting in the coupling of the second nucleoside phosphoramidite onto the 5'-end of the first nucleoside. The support is then washed and any unreacted 5'-hydroxyl groups are capped with a capping reagent such as acetic anhydride to yield inactive 5'-acetyl moieties. The trivalent phosphorus linkage is then oxidized to a more stable phosphate linkage. At the end of the nucleotide addition  
15 cycle, the 5'-O-protecting group is cleaved under suitable conditions (e.g., acidic conditions for trityl-based groups and Fluoride for silyl-based groups). The cycle is repeated for each subsequent nucleotide.

Modification of synthesis conditions can be used to optimize coupling efficiency, for example by using differing coupling times, differing reagent/phosphoramidite  
20 concentrations, differing contact times, differing solid supports and solid support linker chemistries depending on the particular chemical composition of the siNA to be synthesized. Deprotection and purification of the siNA can be performed as is generally described in Deprotection and purification of the siNA can be performed as is generally  
25 described in Usman *et al.*, US 5,831,071, US 6,353,098, US 6,437,117, and Bellon *et al.*, US 6,054,576, US 6,162,909, US 6,303,773, or Scaringe *supra*, incorporated by reference herein in their entireties. Additionally, deprotection conditions can be modified to provide the best possible yield and purity of siNA constructs. For example, applicant has observed that oligonucleotides comprising 2'-deoxy-2'-fluoro nucleotides  
30 can degrade under inappropriate deprotection conditions. Such oligonucleotides are deprotected using aqueous methylamine at about 35°C for 30 minutes. If the 2'-deoxy-

2'-fluoro containing oligonucleotide also comprises ribonucleotides, after deprotection with aqueous methylamine at about 35°C for 30 minutes, TEA-HF is added and the reaction maintained at about 65°C for an additional 15 minutes.

Example 6: RNAi *in vitro* assay to assess siNA activity

- 5        An *in vitro* assay that recapitulates RNAi in a cell-free system is used to evaluate siNA constructs targeting SARS RNA targets. The assay comprises the system described by Tuschl *et al.*, 1999, *Genes and Development*, 13, 3191-3197 and Zamore *et al.*, 2000, *Cell*, 101, 25-33 adapted for use with SARS target RNA. A *Drosophila* extract derived from syncytial blastoderm is used to reconstitute RNAi activity *in vitro*. Target
- 10    RNA is generated via *in vitro* transcription from an appropriate SARS expressing plasmid using T7 RNA polymerase or via chemical synthesis as described herein. Sense and antisense siNA strands (for example 20 uM each) are annealed by incubation in buffer (such as 100 mM potassium acetate, 30 mM HEPES-KOH, pH 7.4, 2 mM magnesium acetate) for 1 minute at 90°C followed by 1 hour at 37°C, then diluted in
- 15    lysis buffer (for example 100 mM potassium acetate, 30 mM HEPES-KOH at pH 7.4, 2mM magnesium acetate). Annealing can be monitored by gel electrophoresis on an agarose gel in TBE buffer and stained with ethidium bromide. The *Drosophila* lysate is prepared using zero to two-hour-old embryos from Oregon R flies collected on yeasted molasses agar that are dechorionated and lysed. The lysate is centrifuged and the
- 20    supernatant isolated. The assay comprises a reaction mixture containing 50% lysate [vol/vol], RNA (10-50 pM final concentration), and 10% [vol/vol] lysis buffer containing siNA (10 nM final concentration). The reaction mixture also contains 10 mM creatine phosphate, 10 ug/ml creatine phosphokinase, 100 uM GTP, 100 uM UTP, 100 uM CTP, 500 uM ATP, 5 mM DTT, 0.1 U/uL RNasin (Promega), and 100 uM of each amino acid.
- 25    The final concentration of potassium acetate is adjusted to 100 mM. The reactions are pre-assembled on ice and preincubated at 25° C for 10 minutes before adding RNA, then incubated at 25° C for an additional 60 minutes. Reactions are quenched with 4 volumes of 1.25 x Passive Lysis Buffer (Promega). Target RNA cleavage is assayed by RT-PCR analysis or other methods known in the art and are compared to control reactions in
- 30    which siNA is omitted from the reaction.

Alternately, internally-labeled target RNA for the assay is prepared by *in vitro* transcription in the presence of [ $\alpha$ - $^{32}$ P] CTP, passed over a G 50 Sephadex column by spin chromatography and used as target RNA without further purification. Optionally, target RNA is 5'- $^{32}$ P-end labeled using T4 polynucleotide kinase enzyme.

5 Assays are performed as described above and target RNA and the specific RNA cleavage products generated by RNAi are visualized on an autoradiograph of a gel. The percentage of cleavage is determined by PHOSPHOR IMAGER<sup>®</sup> (autoradiography) quantitation of bands representing intact control RNA or RNA from control reactions without siNA and the cleavage products generated by the assay.

10 In one embodiment, this assay is used to determine target sites the SARS RNA target for siNA mediated RNAi cleavage, wherein a plurality of siNA constructs are screened for RNAi mediated cleavage of the SARS RNA target, for example, by analyzing the assay reaction by electrophoresis of labeled target RNA, or by northern blotting, as well as by other methodology well known in the art.

15 Example 7: Nucleic acid inhibition of SARS target RNA *in vitro*

siNA molecules targeted to the human SARS RNA are designed and synthesized as described above. These nucleic acid molecules can be tested for cleavage activity *in vivo*, for example, using the following procedure. The target sequences and the nucleotide location within the SARS RNA are given in Table II and III.

20 Two formats are used to test the efficacy of siNAs targeting SARS. First, the reagents are tested in cell culture using, for example, VERO cells and/or FRhk-4 cells, to determine the extent of RNA and protein inhibition. siNA reagents (*e.g.*; see Tables II and III) are selected against the SARS target as described herein. RNA inhibition is measured after delivery of these reagents by a suitable transfection agent to, for example,  
25 VERO cells and/or FRhk-4 cells. Relative amounts of target RNA are measured versus actin using real-time PCR monitoring of amplification (*eg.*, ABI 7700 TAQMAN<sup>®</sup>). A comparison is made to a mixture of oligonucleotide sequences made to unrelated targets or to a randomized siNA control with the same overall length and chemistry, but randomly substituted at each position. Primary and secondary lead reagents are chosen  
30 for the target and optimization performed. After an optimal transfection agent

concentration is chosen, a RNA time-course of inhibition is performed with the lead siNA molecule. In addition, a cell-plating format can be used to determine RNA inhibition.

#### Delivery of siNA to Cells

5        Cells (e.g., VERO cells and/or FRhk-4 cells infected with the SARS virus) are seeded, for example, at  $1 \times 10^5$  cells per well of a six-well dish in EGM-2 (BioWhittaker) the day before transfection. siNA (final concentration, for example 20nM) and cationic lipid (e.g., final concentration 2 $\mu$ g/ml) are complexed in EGM basal media (Bio Whittaker) at 37°C for 30 minutes in polystyrene tubes. Following vortexing, the  
10        complexed siNA is added to each well and incubated for the times indicated. For initial optimization experiments, cells are seeded, for example, at  $1 \times 10^3$  in 96 well plates and siNA complex added as described. Efficiency of delivery of siNA to cells is determined using a fluorescent siNA complexed with lipid. Cells in 6-well dishes are incubated with siNA for 24 hours, rinsed with PBS and fixed in 2% paraformaldehyde for 15 minutes at  
15        room temperature. Uptake of siNA is visualized using a fluorescent microscope.

#### TAQMAN® (real-time PCR monitoring of amplification) and Lightcycler quantification of mRNA

Total RNA is prepared from cells following siNA delivery, for example, using Qiagen RNA purification kits for 6-well or Rneasy extraction kits for 96-well assays. For  
20        TAQMAN® analysis (real-time PCR monitoring of amplification), dual-labeled probes are synthesized with the reporter dye, FAM or JOE, covalently linked at the 5'-end and the quencher dye TAMRA conjugated to the 3'-end. One-step RT-PCR amplifications are performed on, for example, an ABI PRISM 7700 Sequence Detector using 50  $\mu$ l reactions consisting of 10  $\mu$ l total RNA, 100 nM forward primer, 900 nM reverse primer,  
25        100 nM probe, 1X TAQMAN® PCR reaction buffer (PE-Applied Biosystems), 5.5 mM MgCl<sub>2</sub>, 300  $\mu$ M each dATP, dCTP, dGTP, and dTTP, 10U RNase Inhibitor (Promega), 1.25U AMPLITAQ GOLD® (DNA polymerase) (PE-Applied Biosystems) and 10U M-MLV Reverse Transcriptase (Promega). The thermal cycling conditions can consist of 30 minutes at 48°C, 10 minutes at 95°C, followed by 40 cycles of 15 seconds at 95°C  
30        and 1-minute at 60°C. Quantitation of mRNA levels is determined relative to standards

generated from serially diluted total cellular RNA (300, 100, 33, 11 ng/rxn) and normalizing to  $\beta$ -actin or GAPDH mRNA in parallel TAQMAN® reactions (real-time PCR monitoring of amplification). For each gene of interest an upper and lower primer and a fluorescently labeled probe are designed. Real time incorporation of SYBR Green I dye into a specific PCR product can be measured in glass capillary tubes using a lightcycler. A standard curve is generated for each primer pair using control cRNA. Values are represented as relative expression to GAPDH in each sample.

#### Western blotting

Nuclear extracts can be prepared using a standard micro preparation technique (see for example Andrews and Faller, 1991, *Nucleic Acids Research*, 19, 2499). Protein extracts from supernatants are prepared, for example using TCA precipitation. An equal volume of 20% TCA is added to the cell supernatant, incubated on ice for 1 hour and pelleted by centrifugation for 5 minutes. Pellets are washed in acetone, dried and resuspended in water. Cellular protein extracts are run on a 10% Bis-Tris NuPage (nuclear extracts) or 4-12% Tris-Glycine (supernatant extracts) polyacrylamide gel and transferred onto nitro-cellulose membranes. Non-specific binding can be blocked by incubation, for example, with 5% non-fat milk for 1 hour followed by primary antibody for 16 hour at 4°C. Following washes, the secondary antibody is applied, for example (1:10,000 dilution) for 1 hour at room temperature and the signal detected with SuperSignal reagent (Pierce).

#### Example 8: RNAi mediated inhibition of SARS RNA expression

siNA constructs (e.g., siNA constructs shown in Table III) are tested for efficacy in reducing SARS RNA expression in, for example, VERO cells and/or FRhk-4 cells. Cells are plated approximately 24h before transfection in 96-well plates at 5,000-7,500 cells/well, 100  $\mu$ l/well, such that at the time of transfection cells are 70-90% confluent. For transfection, annealed siNAs are mixed with the transfection reagent (Lipofectamine 2000, Invitrogen) in a volume of 50  $\mu$ l/well and incubated for 20 minutes at room temperature. The siNA transfection mixtures are added to cells to give a final siNA concentration of 25 nM in a volume of 150  $\mu$ l. Each siNA transfection mixture is added to 3 wells for triplicate siNA treatments. Cells are incubated at 37° for 24h in the

continued presence of the siNA transfection mixture. At 24h, RNA is prepared from each well of treated cells. The supernatants with the transfection mixtures are first removed and discarded, then the cells are lysed and RNA prepared from each well. Target gene expression following treatment is evaluated by RT-PCR for the target gene and for a control gene (36B4, an RNA polymerase subunit) for normalization. The  
5 triplicate data is averaged and the standard deviations determined for each treatment. Normalized data are graphed and the percent reduction of target mRNA by active siNAs in comparison to their respective inverted control siNAs is determined.

In a non-limiting example, a siNA construct comprising ribonucleotides and 3'-  
10 terminal dithymidine caps is assayed along with a chemically modified siNA construct comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides and purine ribonucleotides in which the sense strand of the siNA is further modified with 5' and 3'-terminal inverted deoxyabasic caps and the antisense strand comprises a 3'-terminal phosphorothioate internucleotide linkage. Additional stabilization chemistries as described in Table IV are  
15 similarly assayed for activity. These siNA constructs are compared to appropriate matched chemistry inverted controls. In addition, the siNA constructs are also compared to untreated cells, cells transfected with lipid and scrambled siNA constructs, and cells transfected with lipid alone (transfection control).

#### Example 9: Animal Models

20 Evaluating the efficacy of anti-SARS agents in animal models is an important prerequisite to human clinical trials. Byron *et al.*, 2003, *Nature*, 425, 915, describe ferret and feline animal models of SARS virus infection. Haagmans *et al.*, 2004, *Nature Medicine*, 10, 290-293, describe the use of pegylated interferon-alpha in protecting type 1 pneumocytes against SARS coronavirus infection in macaques. Gao *et al.*, 2003,  
25 *Lancet*, 362, 1895-6, describe the use of a SARS virus vaccine in monkeys. All of these models can be adapted for use for pre-clinical evaluation of the efficacy of nucleic acid compositions of the invention in modulating SARS virus gene expression toward therapeutic use.

#### Example 10: Indications

The present body of knowledge in SARS research indicates the need for methods to assay SARS activity and for compounds that can regulate SARS expression for research, diagnostic, and therapeutic use. As described herein, the nucleic acid molecules of the present invention can be used in assays to diagnose disease state related  
5 of SARS levels. In addition, the nucleic acid molecules can be used to treat disease state related to SARS levels.

Particular degenerative and disease states that can be associated with SARS expression modulation include, but are not limited to, SARS virus infection, liver failure, hepatocellular carcinoma, cirrhosis, and/or other disease states associated with SARS  
10 virus infection.

Immunomodulators, steroids, and anti-viral compounds are non-limiting examples of pharmaceutical agents that can be combined with or used in conjunction with the nucleic acid molecules (e.g. siNA molecules) of the instant invention. The use of ribavirin and oseltamivir are non-limiting examples of chemotherapeutic agents that can  
15 be combined with or used in conjunction with the nucleic acid molecules (e.g. siNA molecules) of the instant invention. Those skilled in the art will recognize that other anti-cancer compounds and therapies can similarly be readily combined with the nucleic acid molecules of the instant invention (e.g. siNA molecules) and are hence within the scope of the instant invention.

#### 20 Example 11: Interferons

Interferons represent a non-limiting example of a class of compounds that can be used in conjunction with the siNA molecules of the invention for treating the diseases and/or conditions described herein. Type I interferons (IFN) are a class of natural cytokines that includes a family of greater than 25 IFN- $\alpha$  (Pesta, 1986, *Methods*  
25 *Enzymol.* 119, 3-14) as well as IFN- $\beta$ , and IFN- $\omega$ . Although evolutionarily derived from the same gene (Diaz *et al.*, 1994, *Genomics* 22, 540-552), there are many differences in the primary sequence of these molecules, implying an evolutionary divergence in biologic activity. All type I IFN share a common pattern of biologic effects that begin with binding of the IFN to the cell surface receptor (Pfeffer & Strulovici, 1992,  
30 Transmembrane secondary messengers for IFN- $\alpha/\beta$ . In: *Interferon. Principles and*



*Medical Applications.*, S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tying, eds. 151-160). Binding is followed by activation of tyrosine kinases, including the Janus tyrosine kinases and the STAT proteins, which leads to the production of several IFN-stimulated gene products (Johnson *et al.*, 1994, *Sci. Am.* 270, 68-75). The IFN-stimulated gene products are responsible for the pleotropic biologic effects of type I IFN, including antiviral, antiproliferative, and immunomodulatory effects, cytokine induction, and HLA class I and class II regulation (Pestka *et al.*, 1987, *Annu. Rev. Biochem* 56, 727). Examples of IFN-stimulated gene products include 2-5-oligoadenylate synthetase (2-5 OAS),  $\beta_2$ -microglobulin, neopterin, p68 kinases, and the Mx protein (Chebath & Revel, 1992, The 2-5 A system: 2-5 A synthetase, isospecies and functions. In: *Interferon. Principles and Medical Applications*, S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Jr. Fleischmann, T.K. Jr Hughes, G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tying, eds., pp. 225-236; Samuel, 1992, The RNA-dependent P1/eIF-2 $\alpha$  protein kinase. In: *Interferon. Principles and Medical Applications.* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tying, eds. 237-250; Horisberger, 1992, MX protein: function and Mechanism of Action. In: *Interferon. Principles and Medical Applications.* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tying, eds. 215-224). Although all type I IFN have similar biologic effects, not all the activities are shared by each type I IFN, and in many cases, the extent of activity varies quite substantially for each IFN subtype (Fish *et al.*, 1989, *J. Interferon Res.* 9, 97-114; Ozes *et al.*, 1992, *J. Interferon Res.* 12, 55-59). More specifically, investigations into the properties of different subtypes of IFN- $\alpha$  and molecular hybrids of IFN- $\alpha$  have shown differences in pharmacologic properties (Rubinstein, 1987, *J. Interferon Res.* 7, 545-551). These pharmacologic differences can arise from as few as three amino acid residue changes (Lee *et al.*, 1982, *Cancer Res.* 42, 1312-1316).

Eighty-five to 166 amino acids are conserved in the known IFN- $\alpha$  subtypes. Excluding the IFN- $\alpha$  pseudogenes, there are approximately 25 known distinct IFN- $\alpha$  subtypes. Pairwise comparisons of these nonallelic subtypes show primary sequence

differences ranging from 2% to 23%. In addition to the naturally occurring IFNs, a non-natural recombinant type I interferon known as consensus interferon (CIFN) has been synthesized as a therapeutic compound (Tong *et al.*, 1997, *Hepatology* 26, 747-754).

Interferon is currently in use for at least 12 different indications, including  
5 infectious and autoimmune diseases and cancer (Borden, 1992, *N. Engl. J. Med.* 326, 1491-1492). For autoimmune diseases, IFN has been utilized for treatment of rheumatoid arthritis, multiple sclerosis, and Crohn's disease. For treatment of cancer, IFN has been used alone or in combination with a number of different compounds. Specific types of cancers for which IFN has been used include squamous cell  
10 carcinomas, melanomas, hypernephromas, hemangiomas, hairy cell leukemia, and Kaposi's sarcoma. In the treatment of infectious diseases, IFNs increase the phagocytic activity of macrophages and cytotoxicity of lymphocytes and inhibits the propagation of cellular pathogens. Specific indications for which IFN has been used as treatment include hepatitis B, human papillomavirus types 6 and 11 (i.e. genital warts) (Leventhal  
15 *et al.*, 1991, *N Engl J Med* 325, 613-617), chronic granulomatous disease, and SARS virus.

Pegylated interferons, i.e., interferons conjugated with polyethylene glycol (PEG), have demonstrated improved characteristics over interferon. Advantages incurred by PEG conjugation can include an improved pharmacokinetic profile compared to  
20 interferons lacking PEG, thus imparting more convenient dosing regimes, improved tolerance, and improved antiviral efficacy. Such improvements have been demonstrated in clinical studies of both polyethylene glycol interferon alfa-2a (PEGASYS, Roche) and polyethylene glycol interferon alfa-2b (VIRAFERON PEG, PEG-INTRON, Enzon/Schering Plough).

25 siNA molecules in combination with interferons and polyethylene glycol interferons have the potential to improve the effectiveness of treatment of SARS or any of the other indications discussed above. siNA molecules targeting RNAs associated with SARS virus infection can be used individually or in combination with other therapies such as interferons and polyethylene glycol interferons and to achieve  
30 enhanced efficacy.

Example 12: Diagnostic uses

The siNA molecules of the invention can be used in a variety of diagnostic applications, such as in the identification of molecular targets (e.g., RNA) in a variety of applications, for example, in clinical, industrial, environmental, agricultural and/or research settings. Such diagnostic use of siNA molecules involves utilizing reconstituted RNAi systems, for example, using cellular lysates or partially purified cellular lysates. siNA molecules of this invention can be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of endogenous or exogenous, for example viral, RNA in a cell. The close relationship between siNA activity and the structure of the target RNA allows the detection of mutations in any region of the molecule, which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple siNA molecules described in this invention, one can map nucleotide changes, which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with siNA molecules can be used to inhibit gene expression and define the role of specified gene products in the progression of disease or infection. In this manner, other genetic targets can be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple siNA molecules targeted to different genes, siNA molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations siNA molecules and/or other chemical or biological molecules). Other *in vitro* uses of siNA molecules of this invention are well known in the art, and include detection of the presence of mRNAs associated with a disease, infection, or related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a siNA using standard methodologies, for example, fluorescence resonance emission transfer (FRET).

In a specific example, siNA molecules that cleave only wild-type or mutant forms of the target RNA are used for the assay. The first siNA molecules (*i.e.*, those that cleave only wild-type forms of target RNA) are used to identify wild-type RNA present in the sample and the second siNA molecules (*i.e.*, those that cleave only mutant forms of target RNA) are used to identify mutant RNA in the sample. As reaction controls,

synthetic substrates of both wild-type and mutant RNA are cleaved by both siNA molecules to demonstrate the relative siNA efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus, each analysis requires two siNA molecules, two substrates and one unknown sample, which is combined into six reactions. The presence of cleavage products is determined using an RNase protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, disease related or infection related) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels is adequate and decreases the cost of the initial diagnosis. Higher mutant form to wild-type ratios are correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications can be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims. The present invention teaches

one skilled in the art to test various combinations and/or substitutions of chemical modifications described herein toward generating nucleic acid constructs with improved activity for mediating RNAi activity. Such improved activity can comprise improved stability, improved bioavailability, and/or improved activation of cellular responses mediating RNAi. Therefore, the specific embodiments described herein are not limiting and one skilled in the art can readily appreciate that specific combinations of the modifications described herein can be tested without undue experimentation toward identifying siNA molecules with improved RNAi activity.

The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

**Table I: SARS virus Accession Numbers**

5 LOCUS NC\_004718 29736 bp ss-RNA linear VRL 15-APR-2003  
DEFINITION SARS coronavirus, complete genome.  
ACCESSION NC\_004718

(400/110\_US)

Table II: SARS siNA and Target Sequences

SARS CoV NC_004718									
Pos	Seq	Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID	
3	ACCCAGGAAAAGCCAAACA	1	3	ACCCAGGAAAAGCCAAACA	1	21	UGGUUGCUUUUCCUGGGU	1652	
21	AACUCGUAUCUUCUUGAGA	2	21	AACUCGUAUCUUCUUGAGA	2	39	UCUACAAGAGAUCCGAGGUU	1653	
39	AUCUGUUCUUAAGCAAC	3	39	AUCUGUUCUUAAGCAAC	3	57	GUUCGUUUAGAGAACAGAU	1654	
57	CUUUAAAUCUGUGUAGCU	4	57	CUUUAAAUCUGUGUAGCU	4	75	AGCUACACAGAUUUUAAAG	1655	
75	UGUCGUCGGCUGCAUGCC	5	75	UGUCGUCGGCUGCAUGCC	5	93	GGAGCAGCCGAGCGGACA	1656	
93	CUAGUGCACCUCAGCAGUA	6	93	CUAGUGCACCUCAGCAGUA	6	111	UACUGCGUAGGUGGCUAG	1657	
111	AUAAACAUAUAAAUUUU	7	111	AUAAACAUAUAAAUUUU	7	129	AAAUUUUUAUUUUUUUU	1658	
129	UACUGUGGUUGACAAGAA	8	129	UACUGUGGUUGACAAGAA	8	147	UUUCUUGUCAACGACAGUA	1659	
147	ACGAGUAACUCGCCCCUCU	9	147	ACGAGUAACUCGCCCCUCU	9	165	AGAGGGACGAGUUACUCGU	1660	
165	UUCGAGACUGCUUACGG	10	165	UUCGAGACUGCUUACGG	10	183	CCGUAAGCAGUCUGCAGAA	1661	
183	GUUUCGUCGUGUUGCAGU	11	183	GUUUCGUCGUGUUGCAGU	11	201	ACUGCAACACGGACGAAAC	1662	
201	UCGAUCAUCAGCAUACCUA	12	201	UCGAUCAUCAGCAUACCUA	12	219	UAGGUAGCUGAUUGAUGCA	1663	
219	AGGUUUGCGCCGGUGUGA	13	219	AGGUUUGCGCCGGUGUGA	13	237	UCACACCGGACGAAACCU	1664	
237	ACCGAAAGGUAAGUAGG	14	237	ACCGAAAGGUAAGUAGG	14	255	CUCAUCUUUACCUUUUGGU	1665	
255	GAGCCUUGUUCUUGGUGUC	15	255	GAGCCUUGUUCUUGGUGUC	15	273	GACACCAAGAACCAAGGUC	1666	
273	CAACGAGAAACACACGUC	16	273	CAACGAGAAACACACGUC	16	291	GACGGAACACUAGUUGG	1667	
291	CCAACUCAGUUUUGCUGUC	17	291	CCAACUCAGUUUUGCUGUC	17	309	GACAGCAACUAGUUGG	1668	
309	CCUUCAGGUUAGAGACGUG	18	309	CCUUCAGGUUAGAGACGUG	18	327	CACGUCUUAACCUAGAGG	1669	
327	GCUAGUCGUGGCUUCGGG	19	327	GCUAGUCGUGGCUUCGGG	19	345	CCGGAAGCCACGACUAGC	1670	
345	GGACUCUGUGGAGAGGCC	20	345	GGACUCUGUGGAGAGGCC	20	363	GGCCUCUUCACACAGAGUC	1671	
363	CCUUCGAGGACGUGAA	21	363	CCUUCGAGGACGUGAA	21	381	UUCACGUGCCUCCGUAUGG	1672	
381	ACACCUCAAAAUGGCACU	22	381	ACACCUCAAAAUGGCACU	22	399	AGUGCCAUUUUUGAGGUGU	1673	
399	UUGUGGUCUAGUAGCGUG	23	399	UUGUGGUCUAGUAGCGUG	23	417	CAGCUCUACUAGACCCAA	1674	
417	GGAAAAAGGCGUACUGCCC	24	417	GGAAAAAGGCGUACUGCCC	24	435	GGCGAGUACGCUUUUCC	1675	
435	CCAGCUUAGAACAGCCUUAU	25	435	CCAGCUUAGAACAGCCUUAU	25	453	AUAGGCGUGUUAAGCUGG	1676	
453	UGUGUUCAUUAAACGUUCU	26	453	UGUGUUCAUUAAACGUUCU	26	471	AGAACGUUUAUAGAACACA	1677	
471	UGAUGCCUUAAGCACCAU	27	471	UGAUGCCUUAAGCACCAU	27	489	AUUGGUGCUUAAGGCAUCA	1678	
489	UCACGGCCACAGGUCGUU	28	489	UCACGGCCACAGGUCGUU	28	507	AACGACCUUGUGGCCGUGA	1679	
507	UGAGCUUGUUGCAGAAUUG	29	507	UGAGCUUGUUGCAGAAUUG	29	525	CAUUCUGCAACCCAGCUCA	1680	
525	GGACGGCAUUCAGUACGGU	30	525	GGACGGCAUUCAGUACGGU	30	543	ACCGUACUGAAUCCCGUCC	1681	
543	UCGUAGCGGUUAUACACUG	31	543	UCGUAGCGGUUAUACACUG	31	561	CAGUGUUAUACCGCUACGA	1682	
561	GGGAGUACUCUGGCCACAU	32	561	GGGAGUACUCUGGCCACAU	32	579	AUGUGGACGAGUACUCCC	1683	
579	UGUGGGCGAAACCCCAU	33	579	UGUGGGCGAAACCCCAU	33	597	AUUGGGGUUUCGCCACA	1684	
597	UGCAUACCGCAAUUUCU	34	597	UGCAUACCGCAAUUUCU	34	615	AAGAACAUUCGCUAUGCA	1685	
615	UCUUCGUAAGACGGUAAU	35	615	UCUUCGUAAGACGGUAAU	35	633	AUACCGUUCUACGAAGA	1686	
633	UAAGGGAGCCGGUGGUCAU	36	633	UAAGGGAGCCGGUGGUCAU	36	651	AUGACCACCGGCCUCCUUA	1687	

(400/110\_US)

651	UAGCUAUGGCAUCUA	37	651	UAGCUAUGGCAUCUA	37	669	UAGCUAUGGCAUCUA	1688
669	AAAGUCUUAAGCUUAGGU	38	669	AAAGUCUUAAGCUUAGGU	38	687	ACCUAAGUCUUAAGCUU	1689
687	UACGAGCUUUGGACUGAU	39	687	UACGAGCUUUGGACUGAU	39	705	AUCAGUGCCAAAGCUCUCA	1690
705	UCCCAUUGAAGAUUAUGAA	40	705	UCCCAUUGAAGAUUAUGAA	40	723	UUCAUAUCUUAAGGGA	1691
723	ACAAACUGGAACACUAAG	41	723	ACAAACUGGAACACUAAG	41	741	CUUAGUUCUCCAGUUUUGU	1692
741	GCAUGGCAUGGUGGACUC	42	741	GCAUGGCAUGGUGGACUC	42	759	GAGUGCAUCUCCGACG	1693
759	CCGUAACUACUCUGAG	43	759	CCGUAACUACUCUGAG	43	777	CUCACGAGUAGUCCAGG	1694
777	GCUCUAUGGAGUGCAGUC	44	777	GCUCUAUGGAGUGCAGUC	44	795	GACUGCACUCCAUUGAGC	1695
795	CACUCGCUAUGUGGACAA	45	795	CACUCGCUAUGUGGACAA	45	813	GUUGUGGACUAGCGAGUG	1696
813	CAUUAUCUGUGGCCAGAU	46	813	CAUUAUCUGUGGCCAGAU	46	831	AUCUGGCCAGGAAUUG	1697
831	UGGUAACCCUUGAUUGC	47	831	UGGUAACCCUUGAUUGC	47	849	GCAUCAAAGGAGGUAUCCCA	1698
849	CAUCAAGAUUUUCGCA	48	849	CAUCAAGAUUUUCGCA	48	867	UGCAGAAAUUUUUGAUG	1699
867	ACGCGCGGCAAGUCAAUG	49	867	ACGCGCGGCAAGUCAAUG	49	885	CAUUGACUUGCCCGCGGU	1700
885	GUGCACUUCUCCGAACAA	50	885	GUGCACUUCUCCGAACAA	50	903	UUUUCGGAAGAGUGCAC	1701
903	ACUUGAUUAUCGAGUCG	51	903	ACUUGAUUAUCGAGUCG	51	921	GCACUCGAGUUAUUAAGU	1702
921	GAAGAGGUGUUAUCUGC	52	921	GAAGAGGUGUUAUCUGC	52	939	GCAGUAGACACCUUCUUC	1703
939	CUGCGUGACCAUAGCAU	53	939	CUGCGUGACCAUAGCAU	53	957	AUGCUCUUGGACGCGCAG	1704
957	UGAAUUGCCUGGUUACU	54	957	UGAAUUGCCUGGUUACU	54	975	AGUGAACCAAGCAAUUUA	1705
975	UGAGCGCUCUGUAAGAGC	55	975	UGAGCGCUCUGUAAGAGC	55	993	GCUCUUAUCAGAGCGCUCA	1706
993	CUACGAGCAGACACGCC	56	993	CUACGAGCAGACACGCC	56	1011	GGUGUGUGGUGGUGGUG	1707
1011	CUUGCAUUAAGAGUCG	57	1011	CUUGCAUUAAGAGUCG	57	1029	GGCACUCUUAUUAUUGAAG	1708
1029	CAAGAAUUAACACUUC	58	1029	CAAGAAUUAACACUUC	58	1047	GAAAGUGCAAAUUCUUG	1709
1047	CAAAGGGAAUGCCCAAG	59	1047	CAAAGGGAAUGCCCAAG	59	1065	CUUUGGCAUUCUCCUUG	1710
1065	GUUUGUUAUCCUUAAC	60	1065	GUUUGUUAUCCUUAAC	60	1083	GUUAAGAGGAACACAAAC	1711
1083	CUCAAAAGUCAAAGUCAAU	61	1083	CUCAAAAGUCAAAGUCAAU	61	1101	AAUGACUUAAGCUUUUUGAG	1712
1101	UCAACCAAGUUAAGAAAG	62	1101	UCAACCAAGUUAAGAAAG	62	1119	CUUUUACACGUGGUGUA	1713
1119	GAAAAGACUGAGGUGUUC	63	1119	GAAAAGACUGAGGUGUUC	63	1137	GAAACCCUACUUCUUC	1714
1137	CAUGGGCGUAUACGCUUC	64	1137	CAUGGGCGUAUACGCUUC	64	1155	AGACGUAUACGCCCAUG	1715
1155	UGUGUACCCUGUUGCAUCU	65	1155	UGUGUACCCUGUUGCAUCU	65	1173	AGAGCAACAGGUGUACACA	1716
1173	UCCACAGGAGUUAACAAU	66	1173	UCCACAGGAGUUAACAAU	66	1191	AUUGUUAACUCCUGGGA	1717
1191	UAUGCACUUGUUAACCUUG	67	1191	UAUGCACUUGUUAACCUUG	67	1209	CAAGGUAGACAAGUGCAUA	1718
1209	GAUGAAUUAUUAUUGC	68	1209	GAUGAAUUAUUAUUGC	68	1227	GCAUUAUUAUUAUUAUUAUC	1719
1227	CGAUGAAGUUAUUAUGCAG	69	1227	CGAUGAAGUUAUUAUGCAG	69	1245	GUCCCAUGAAACUUAUUAUCG	1720
1245	GAGGUGCGAUUUAUGAAU	70	1245	GAGGUGCGAUUUAUGAAU	70	1263	UUUCAGAAAGUGGACGUC	1721
1263	AGCCACUUGUAACAUUGU	71	1263	AGCCACUUGUAACAUUGU	71	1281	ACAAUUAUUAUUAUUAUUAUC	1722
1281	UGGACUGAAAUUAUUAUUGU	72	1281	UGGACUGAAAUUAUUAUUGU	72	1299	AACUAAUUAUUAUUAUUAUUAUC	1723
1299	UAUUAAGGACCUUAUUAUUA	73	1299	UAUUAAGGACCUUAUUAUUA	73	1317	AGUAGGUGGUUUAUUAUUAUUAUC	1724
1317	UAUUAAGGACCUUAUUAUUA	74	1317	UAUUAAGGACCUUAUUAUUA	74	1335	AGUAGGUGGUUUAUUAUUAUUAUC	1725
1335	UAUUAAGGACCUUAUUAUUA	75	1335	UAUUAAGGACCUUAUUAUUA	75	1353	CAUUAUUAUUAUUAUUAUUAUC	1726
1353	UAUUAAGGACCUUAUUAUUA	76	1353	UAUUAAGGACCUUAUUAUUA	76	1371	UUGACAGGCGGACAUUGGC	1727
1371	AGACCCAGAGUUAUGGACCU	77	1371	AGACCCAGAGUUAUGGACCU	77	1389	AGGUCCAAUUAUUAUUAUUAUC	1728
1389	UGAGCAUUAUGUUAUGGACCU	78	1389	UGAGCAUUAUGUUAUGGACCU	78	1407	AUCUGCAACACUUAUGGACCU	1729



(400/110\_US)

1407	UUUACACAAACACUCAAAC	79	1407	UUUACACAAACACUCAAAC	79	1425	GUUUGAGUGGUUGUUAAG	1730
1425	CAUUGAAACUCGACUCCGC	80	1425	CAUUGAAACUCGACUCCGC	80	1443	GCGGAGUCGAGUUAUAAAG	1731
1443	CAAGGGAGGUAGGACUAGA	81	1443	CAAGGGAGGUAGGACUAGA	81	1461	UCUAGUCUACCUCCUUG	1732
1461	AUGUUUUGGAGGUGUGUG	82	1461	AUGUUUUGGAGGUGUGUG	82	1479	CACACAGCCUCCAAAGAU	1733
1479	GUUUGCCUAGUUGGUGUG	83	1479	GUUUGCCUAGUUGGUGUG	83	1497	GCAGCCAAACUAGGCAAC	1734
1497	CUAUAUAAGCGUGCCUAC	84	1497	CUAUAUAAGCGUGCCUAC	84	1515	GUAGGACGCUUAUUAUAG	1735
1515	CUGGUGUCCUGUGUAGU	85	1515	CUGGUGUCCUGUGUAGU	85	1533	ACUAGCAGGAGGACCCAG	1736
1533	UGUGAUUAUUGGUCAGGC	86	1533	UGUGAUUAUUGGUCAGGC	86	1551	GCCUGAGCCAAUAUCAGCA	1737
1551	CCAUAUGGCAUAUACUGGU	87	1551	CCAUAUGGCAUAUACUGGU	87	1569	ACCAGUAUUGCCAGUAUGG	1738
1569	UGACAAGUGGAGACCUUG	88	1569	UGACAAGUGGAGACCUUG	88	1587	CAAGGUCUACCAUUGUCA	1739
1587	GAUAGGAGUCCUUGAG	89	1587	GAUAGGAGUCCUUGAG	89	1605	CUAAGGAGACCUCAUUC	1740
1605	GAUACUGAGUCUGAACGU	90	1605	GAUACUGAGUCUGAACGU	90	1623	ACGUUACGACUCAGUAUC	1741
1623	UGUAACAUUAACAUUGUU	91	1623	UGUAACAUUAACAUUGUU	91	1641	AACAUGUUAUUGUUAAGA	1742
1641	UGGCGAUUAUUAUUGAAU	92	1641	UGGCGAUUAUUAUUGAAU	92	1659	AUUCAAAUAGAAAUUGCCA	1743
1659	UGAAGAGGUUGCCAUCAUU	93	1659	UGAAGAGGUUGCCAUCAUU	93	1677	AUGAUGGCAACCUCAUCA	1744
1677	UUUGGCAUCUUCUCUGCU	94	1677	UUUGGCAUCUUCUCUGCU	94	1695	AGCAGAGAAAGAUUGCCAAA	1745
1695	UUCUACAAGUGCCUUAUU	95	1695	UUCUACAAGUGCCUUAUU	95	1713	AUUAAGGACUUGUAGAA	1746
1713	UGACACUAUAAAGAGUCUU	96	1713	UGACACUAUAAAGAGUCUU	96	1731	AAGACUCUUAUAGUGUCA	1747
1731	UGAUUACAAGUCUUAUCAA	97	1731	UGAUUACAAGUCUUAUCAA	97	1749	UUUGAAAGACUUGUAUACA	1748
1749	AACCAUUGUAGUCCUGC	98	1749	AACCAUUGUAGUCCUGC	98	1767	GCAGGACUACAUAUGGUU	1749
1767	CGUAACUAUAAAGUUAACC	99	1767	CGUAACUAUAAAGUUAACC	99	1785	GGUAACUUAUAGUUAUCCG	1750
1785	CAAGGAAAGCCCGUAAAA	100	1785	CAAGGAAAGCCCGUAAAA	100	1803	UUUUACGGCUUUCUCCUUG	1751
1803	AGGUGCUUGGAACAUUGGA	101	1803	AGGUGCUUGGAACAUUGGA	101	1821	UCCAUGUUCUCAAAGCACC	1752
1821	ACAACAGAGUACAGUUUUA	102	1821	ACAACAGAGUACAGUUUUA	102	1839	UAAAACUGAUCUCUGUUGU	1753
1839	AACACCAUGUGUGUUUUU	103	1839	AACACCAUGUGUGUUUUU	103	1857	AAACCCACACAGUGGUGUU	1754
1857	UCCUCACAGGCGUGUGU	104	1857	UCCUCACAGGCGUGUGU	104	1875	ACCAGCAGCUGUGAGGGA	1755
1875	UGUUAUCAGAUCAUUUUU	105	1875	UGUUAUCAGAUCAUUUUU	105	1893	AAAAUUGAUCUGUAUACA	1756
1893	UGCGGCACACUUGAUGCA	106	1893	UGCGGCACACUUGAUGCA	106	1911	UGCAUCAAGUGUGCGCGCA	1757
1911	AGCAAACCAUCUAAUCCU	107	1911	AGCAAACCAUCUAAUCCU	107	1929	AGGAUUGAGUGGUUUGCU	1758
1929	UGAUUUGCAAAGAGCAGCU	108	1929	UGAUUUGCAAAGAGCAGCU	108	1947	AGCUGCUCUUAUGCAAUUA	1759
1947	UGUCACCAUACUUGAUGGU	109	1947	UGUCACCAUACUUGAUGGU	109	1965	ACCAUCAAGUUGGUGACA	1760
1965	UAUUUCUAGAACAGUUAUA	110	1965	UAUUUCUAGAACAGUUAUA	110	1983	UAUUGACUGUUCAGAAUA	1761
1983	ACGUCUUGUGCGACGCCAUG	111	1983	ACGUCUUGUGCGACGCCAUG	111	2001	CAUGGCGUCGACAAGACGU	1762
2001	GGUUUAUACUUCAGACCUUG	112	2001	GGUUUAUACUUCAGACCUUG	112	2019	CAGGUCUGAAGUAUAAACC	1763
2019	GCUCACCAACAGUGUCAUU	113	2019	GCUCACCAACAGUGUCAUU	113	2037	AUUGACACUGUUGGUGAGC	1764
2037	UAUUAUGGCAUAUUGUAACU	114	2037	UAUUAUGGCAUAUUGUAACU	114	2055	AGUUAUAUUGCCAUUAUA	1765
2055	UGGUGGUCUUGUACAACAG	115	2055	UGGUGGUCUUGUACAACAG	115	2073	CUGUUGUACAAGACCCCA	1766
2073	GACUUCUCAGGUGGUUGUCU	116	2073	GACUUCUCAGGUGGUUGUCU	116	2091	AGACAACCAUCAGAGAGUC	1767
2091	UAUUCUUAUGGCGACUACU	117	2091	UAUUCUUAUGGCGACUACU	117	2109	AGUAGUCCCAAAAGAUUA	1768
2109	UUUGGAAUUAACUAGGCGCU	118	2109	UUUGGAAUUAACUAGGCGCU	118	2127	AGGCCUGAGUUUUUCAACA	1769
2127	UAUCUUUGAAUGGUAUUGAG	119	2127	UAUCUUUGAAUGGUAUUGAG	119	2145	CUCAAUCCAUUCAAAGAUUA	1770
2145	GGCGAAACUUAUGGCGAGGA	120	2145	GGCGAAACUUAUGGCGAGGA	120	2163	UCCUGCACUAAGUUUGGCC	1771

(400/110\_US)

2163	AGUUGAAUUCUCAAGGAU	121	2163	AGUUGAAUUCUCAAGGAU	121	2181	AUCCUUGAGAAUUCACU	1772
2181	UGCUUGGGAGAUUCUCAA	122	2181	UGCUUGGGAGAUUCUCAA	122	2199	UUUGAGAUUCUCCAAAGCA	1773
2199	AUUUCUUAUACAGGUGU	123	2199	AUUUCUUAUACAGGUGU	123	2217	AACACCGAUUAGAGAAA	1774
2217	UUUGACAUUCGUAAGGUGU	124	2217	UUUGACAUUCGUAAGGUGU	124	2235	ACCCUUGACGUAUGCAAAA	1775
2235	UCAAUACACGUGUUCUUA	125	2235	UCAAUACACGUGUUCUUA	125	2253	UGAAGCAACCGUAUUUGA	1776
2253	AGAAUACUACAGGAUUGU	126	2253	AGAAUACUACAGGAUUGU	126	2271	ACAAUCCUUGUUAUUCU	1777
2271	UGUAAAUGCUUUAUUGAU	127	2271	UGUAAAUGCUUUAUUGAU	127	2289	AUCAUUGAAGCAUUUUA	1778
2289	UGUUGUUAACAAGGCACUC	128	2289	UGUUGUUAACAAGGCACUC	128	2307	GAGUGCUUUGUUAACAACA	1779
2307	CGAAUUGUGCAUUGAUCAA	129	2307	CGAAUUGUGCAUUGAUCAA	129	2325	UUUGACUUAUGCAUUCG	1780
2325	AGUCACUUAUCGUGGCGCA	130	2325	AGUCACUUAUCGUGGCGCA	130	2343	UGCGCGAGCGAUAGUGACU	1781
2343	AAAGUUGCGAUCACUAAAC	131	2343	AAAGUUGCGAUCACUAAAC	131	2361	GUUGAGUGAUCGCAACUUA	1782
2361	CUUAGGUGAAGUCUUAUC	132	2361	CUUAGGUGAAGUCUUAUC	132	2379	GUAAGAACUUAACCUAAG	1783
2379	CGCUCAAAGCAAGGACUUA	133	2379	CGCUCAAAGCAAGGACUUA	133	2397	AAGUCCUUGCUUUGAGCG	1784
2397	UUACCGUACAGUUAUACCU	134	2397	UUACCGUACAGUUAUACCU	134	2415	ACGUUACACUGACGGUAA	1785
2415	UGGCAAGGAGCAGCUGCAA	135	2415	UGGCAAGGAGCAGCUGCAA	135	2433	UUGCAGCUUGCUUUGCCA	1786
2433	ACUACUUAUCCUUAAG	136	2433	ACUACUUAUCCUUAAG	136	2451	CUUAAAGGCAUUGAGUAGU	1787
2451	GGCACCAAAAGUAACCC	137	2451	GGCACCAAAAGUAACCC	137	2469	GGUUAUUCUUAUUGGUGCC	1788
2469	CUUUCUUAAGGUAUUA	138	2469	CUUUCUUAAGGUAUUA	138	2487	UGAAUACCUUUAAGAAAG	1789
2487	ACAUGACACAGUUAUAC	139	2487	ACAUGACACAGUUAUAC	139	2505	GGUAAUACUGUGUUAUGU	1790
2505	CUCUGAGGAGGUGUUCUC	140	2505	CUCUGAGGAGGUGUUCUC	140	2523	GAGAAACCCUCCUAGAG	1791
2523	CAAGAACGGUAGACUCGAA	141	2523	CAAGAACGGUAGACUCGAA	141	2541	UUCGAGUUAACCGUUCUUG	1792
2541	AGCACUUAUAAAGGUGUA	142	2541	AGCACUUAUAAAGGUGUA	142	2559	AACGGGCGUCUGAGUGCU	1793
2559	UGAUAGCUUACAAUUGGA	143	2559	UGAUAGCUUACAAUUGGA	143	2577	UCCAUUUGUAAGCUUA	1794
2577	AGCUAUCGUGGACACCA	144	2577	AGCUAUCGUGGACACCA	144	2595	UGGUGUGCGGACGAUAGCU	1795
2595	AGUCUGUGUAAUUGGCCUC	145	2595	AGUCUGUGUAAUUGGCCUC	145	2613	GAGGCCAUUUAACACAGCU	1796
2613	CAUGCUCUUAAGAGAUUAG	146	2613	CAUGCUCUUAAGAGAUUAG	146	2631	CUUAAUUCUUAAGAGCAUG	1797
2631	GGACAAAGAACAAUACUC	147	2631	GGACAAAGAACAAUACUC	147	2649	GCAGUUAUUCUUAUUGCC	1798
2649	CGCAUUGUCUCCUGGUUA	148	2649	CGCAUUGUCUCCUGGUUA	148	2667	UAAACGAGGACAAUUGCG	1799
2667	ACUGGCUAACAACAUAUUC	149	2667	ACUGGCUAACAACAUAUUC	149	2685	GACAUUUGUUAUGCCAGU	1800
2685	CUUUCGCUUAAAGGGGUGU	150	2685	CUUUCGCUUAAAGGGGUGU	150	2703	ACCCCUUUAUAAAGCGAAAG	1801
2703	UGCACCAUUAAGGUGUA	151	2703	UGCACCAUUAAGGUGUA	151	2721	UACACCUUUAUUGGUGCA	1802
2721	AACCUUUGGAGAGAUACU	152	2721	AACCUUUGGAGAGAUACU	152	2739	AGUAUUCUCCAAAGGUGU	1803
2739	UGUUGGGAGUUAACAAGGU	153	2739	UGUUGGGAGUUAACAAGGU	153	2757	ACCUUGAACUCCCAACA	1804
2757	UUAACAAGAUUGAGAAUC	154	2757	UUAACAAGAUUGAGAAUC	154	2775	GAUUCUACAUCUUAUUA	1805
2775	CACAUUUGAGCUUUGAUA	155	2775	CACAUUUGAGCUUUGAUA	155	2793	UUAACAAGCUCAAAUUGUG	1806
2793	ACGUGUUAACAAGGUGCUU	156	2793	ACGUGUUAACAAGGUGCUU	156	2811	AAGCACUUAUGCAACACGU	1807
2811	UAUUGAAAGGUGCUCUCUC	157	2811	UAUUGAAAGGUGCUCUCUC	157	2829	GACAGACGACUUAUUA	1808
2829	CUACACUGUUAUUAUCCGUGU	158	2829	CUACACUGUUAUUAUCCGUGU	158	2847	ACCGAUUUAACAACAGUGUAG	1809
2847	UACCGAAGUUAUUAUCCGUGU	159	2847	UACCGAAGUUAUUAUCCGUGU	159	2865	AAACUGCUAUAUCCGUGU	1810
2865	UGCAUGUGUUAUUAUCCGAG	160	2865	UGCAUGUGUUAUUAUCCGAG	160	2883	CUCUGCUAUAUCCGUGU	1811
2883	GGCUGUUAUUAUCCGAG	161	2883	GGCUGUUAUUAUCCGAG	161	2901	UAAAGUUAUUAUCCGAG	1812
2901	ACAACCAAGUUAUUAUCCGAG	162	2901	ACAACCAAGUUAUUAUCCGAG	162	2919	GAGAUCAAGAAUCCGUGU	1813

(400/110\_US)

2919	CCUUAACCAACAUUGGUAUU	163	2919	CCUUAACCAACAUUGGUAUU	163	2937	AAUACCAUUGUUAAGG	1814
2937	UGAUCUUGAGUGGAGU	164	2937	UGAUCUUGAGUGGAGU	164	2955	ACUCCACUACAAGAUCA	1815
2955	UGUAGCUACAUUUAUUA	165	2955	UGUAGCUACAUUUAUUA	165	2973	UAGUAGAAUGUAGCUACA	1816
2973	AUUUGAUGUGGUGGAA	166	2973	AUUUGAUGUGGUGGAA	166	2991	UUCACAGCAUCAUCAAU	1817
2991	AGAAACUUUUAUUAUUA	167	2991	AGAAACUUUUAUUAUUA	167	3009	ACGUAUGAAAUUUUUU	1818
3009	UAUUAUUGUCCUUUAU	168	3009	UAUUAUUGUCCUUUAU	168	3027	GUAAAGGAACAUAUUA	1819
3027	CCUCCAGAUAGGAGAA	169	3027	CCUCCAGAUAGGAGAA	169	3045	UUCUUCUACUUGGAGG	1820
3045	AGAGGACGAUGCAGAGU	170	3045	AGAGGACGAUGCAGAGU	170	3063	ACACUUGCAUGGUCCU	1821
3063	UGAGGAAGAAGAAUUAU	171	3063	UGAGGAAGAAGAAUUAU	171	3081	AUCAUUUUAUUAUUA	1822
3081	UGAAACCUUGAACAUGAG	172	3081	UGAAACCUUGAACAUGAG	172	3099	CUCAUUGCACAGGUUA	1823
3099	GUACGGUACAGAGGAU	173	3099	GUACGGUACAGAGGAU	173	3117	AUCAUCCUGUAGCCGU	1824
3117	UUAUCAAAGGUCUCCUCU	174	3117	UUAUCAAAGGUCUCCUCU	174	3135	CAGAGGAGACCUUGAU	1825
3135	GGAAUUUGGUCUACGCU	175	3135	GGAAUUUGGUCUACGCU	175	3153	AGCUGAGGCACCAAUU	1826
3153	UGAAACAGUUGGAGUAG	176	3153	UGAAACAGUUGGAGUAG	176	3171	CUCAACUGAAACUUAU	1827
3171	GGAAAGAAGAGGAAGAC	177	3171	GGAAAGAAGAGGAAGAC	177	3189	GUCUUCUUAUUAUUA	1828
3189	CUGGCUAGAUUAUUAU	178	3189	CUGGCUAGAUUAUUAU	178	3207	AGUAGUAUUAUUAUUA	1829
3207	UGAGCAUUAUUAUUAU	179	3207	UGAGCAUUAUUAUUAU	179	3225	CUCAUUCUGAUUAUUA	1830
3225	GCCAGAACCAACCUUA	180	3225	GCCAGAACCAACCUUA	180	3243	UGUAGGUUUGGUUGG	1831
3243	ACCUGAAGAACCAUUAU	181	3243	ACCUGAAGAACCAUUAU	181	3261	AUUAACUGGUUUAUUA	1832
3261	UCAGUUUAUUAUUAU	182	3261	UCAGUUUAUUAUUAU	182	3279	UAAUUAACCAUUAUUA	1833
3279	AAACUUUAUUAUUAU	183	3279	AAACUUUAUUAUUAU	183	3297	AACAUUGCAGUAUUAU	1834
3297	UGCCAUUAUUAUUAU	184	3297	UGCCAUUAUUAUUAU	184	3315	GUCAACACAUUAUUAU	1835
3315	CAUCGUUAUUAUUAU	185	3315	CAUCGUUAUUAUUAU	185	3333	UUGUGCCUUAUUAUUA	1836
3333	AAGUGCUAAUUAUUAU	186	3333	AAGUGCUAAUUAUUAU	186	3351	CACCAUAGGAUUAUUA	1837
3351	GAUUGUAAUUAUUAU	187	3351	GAUUGUAAUUAUUAU	187	3369	GUUAGCAGAUUAUUAU	1838
3369	CAUACACCUAAUUAUUA	188	3369	CAUACACCUAAUUAUUA	188	3387	ACCAUUGUUAUUAUUA	1839
3387	UGGUGGUUAUUAUUAU	189	3387	UGGUGGUUAUUAUUAU	189	3405	UGCACCUGUAUUAUUA	1840
3405	ACUCAACAGGCAUUAU	190	3405	ACUCAACAGGCAUUAU	190	3423	AUUGGUUUAUUAUUA	1841
3423	UGGUGCCAUUAUUAUUA	191	3423	UGGUGCCAUUAUUAUUA	191	3441	CUCUUAUUAUUAUUA	1842
3441	GAGUGAUUAUUAUUAU	192	3441	GAGUGAUUAUUAUUAU	192	3459	CUUAUUAUUAUUAUUA	1843
3459	GCUAUUAUUAUUAUUA	193	3459	GCUAUUAUUAUUAUUA	193	3477	UGUAAGAGGCAUUAUUA	1844
3477	AGUAGGAGGCUUAUUAU	194	3477	AGUAGGAGGCUUAUUAU	194	3495	CAACAAGACCCUUAUUA	1845
3495	GCUUUCUGGACAUUAUUA	195	3495	GCUUUCUGGACAUUAUUA	195	3513	AAGAUUAUUAUUAUUA	1846
3513	UGCUAAGAAGUGUUAUUA	196	3513	UGCUAAGAAGUGUUAUUA	196	3531	AUGCAGACAUUAUUAUUA	1847
3531	UGUUGUUGGACCUUAUUA	197	3531	UGUUGUUGGACCUUAUUA	197	3549	UAGGUUAGGCUUAUUAU	1848
3549	AAUUGCAGGUGGACAUUA	198	3549	AAUUGCAGGUGGACAUUA	198	3567	GAUGUCCUUAUUAUUAU	1849
3567	CCAGCUUAUUAUUAUUA	199	3567	CCAGCUUAUUAUUAUUA	199	3585	UGCUGCCUUAUUAUUAU	1850
3585	AUAUUAUUAUUAUUAUUA	200	3585	AUAUUAUUAUUAUUAUUA	200	3603	UGAAUUAUUAUUAUUAU	1851
3603	ACAGGACAUUAUUAUUA	201	3603	ACAGGACAUUAUUAUUA	201	3621	UGCAAGUAUUAUUAUUAU	1852
3621	ACCAUUGUUAUUAUUAUUA	202	3621	ACCAUUGUUAUUAUUAUUA	202	3639	GCCUGCAGCAUUAUUAUUA	1853
3639	CAUUAUUGGCUUAUUAUUA	203	3639	CAUUAUUGGCUUAUUAUUA	203	3657	UGGUUUAUUAUUAUUAUUA	1854
3657	ACUUCAGUCUUAUUAUUAUUA	204	3657	ACUUCAGUCUUAUUAUUAUUA	204	3675	CACUUGUAUUAUUAUUAUUA	1855

(400/110\_US)

3675	GUGCGUGGACAGCGGUUCGU	205	3675	GUGCGUGGACAGCGGUUCGU	205	3693	ACGAACCGUCUGCAGCGAC	1856
3693	UACACAGGUUUAUUGCA	206	3693	UACACAGGUUUAUUGCA	206	3711	UGCAUUAUAAACCGUGUA	1857
3711	AGUCAAUGACAAAGCUCU	207	3711	AGUCAAUGACAAAGCUCU	207	3729	AAGAGCUUUGUCAUUGACU	1858
3729	UUAUGAGCAGGUUGUCAUG	208	3729	UUAUGAGCAGGUUGUCAUG	208	3747	CAUGACAACCGUCUCAUAA	1859
3747	GGAUUAUCUUGAUAAACUG	209	3747	GGAUUAUCUUGAUAAACUG	209	3765	CAGGUUAUCAAGAUAAUCC	1860
3765	GAAGCCUAGAGUGGAAGCA	210	3765	GAAGCCUAGAGUGGAAGCA	210	3783	UGCUCCACUCUAGGCUUC	1861
3783	ACCUAAACAAGAGGAGCA	211	3783	ACCUAAACAAGAGGAGCA	211	3801	UGGCUCCUUGUUUAGGU	1862
3801	ACCAACACAGAGAUAUCC	212	3801	ACCAACACAGAGAUAUCC	212	3819	GGAUUCUUCUGUGUUGGU	1863
3819	CAAAACUGAGGAGAAUUC	213	3819	CAAAACUGAGGAGAAUUC	213	3837	AGAUUCUCCUCAGUUUUG	1864
3837	UGUCGUACAGAGCCUGUC	214	3837	UGUCGUACAGAGCCUGUC	214	3855	GACAGCUUCUGUACGACA	1865
3855	CGAUGAGAGCCAAAUAU	215	3855	CGAUGAGAGCCAAAUAU	215	3873	AAUUUUUGGUUCACAUCC	1866
3873	UAAGGCCUGCAUUGAUGAG	216	3873	UAAGGCCUGCAUUGAUGAG	216	3891	CUCAUAAUGCAGGCGCUUA	1867
3891	GGUUAACCAACACUGGAA	217	3891	GGUUAACCAACACUGGAA	217	3909	UUCAGUGUUGUGUAACC	1868
3909	AGAAACUAAAGUUUCUUAAC	218	3909	AGAAACUAAAGUUUCUUAAC	218	3927	GGUAAAGAAACUUAGUUUCU	1869
3927	CAUAAGUUAUCUCUUGUU	219	3927	CAUAAGUUAUCUCUUGUU	219	3945	AAACAAGAGUAACUUAUUG	1870
3945	UGCUGAUUAUUAUUAAG	220	3945	UGCUGAUUAUUAUUAAG	220	3963	CUUACCAUUGAUUAUUAAG	1871
3963	GCUUUACCAUUAUUAUUAAG	221	3963	GCUUUACCAUUAUUAUUAAG	221	3981	CUGAAAUCAUGGUAAGC	1872
3981	GAACAUGCUUAUGGUAAG	222	3981	GAACAUGCUUAUGGUAAG	222	3999	UUCACCUUAAGCAUUGUC	1873
4017	GAAGGAGCAGCUUAUUAAG	223	4017	GAAGGAGCAGCUUAUUAAG	223	4035	CAUGAAAGGUGCAUCCUUC	1874
4035	GGUAGGUGAUGUUAUUAAG	224	4035	GGUAGGUGAUGUUAUUAAG	224	4053	AGUAAUAAUUAUUAUUAAG	1875
4053	UAGUGGUGAUAUUAUUAAG	225	4053	UAGUGGUGAUAUUAUUAAG	225	4071	ACAAGUAAUUAUUAUUAAG	1876
4071	UAGUGGUGAUAUUAUUAAG	226	4071	UAGUGGUGAUAUUAUUAAG	226	4089	UUUGGAGGUAUUAUUAAG	1877
4089	AAAGGCGUGGUGGACUUAU	227	4089	AAAGGCGUGGUGGACUUAU	227	4107	AGUAGUGGACGACCUUUA	1878
4107	UGAGAUGCUCUUAUUAAG	228	4107	UGAGAUGCUCUUAUUAAG	228	4125	AGCUUUGAGCAUUAUUAAG	1879
4125	UUUGAAGAAAGUGGACUUA	229	4125	UUUGAAGAAAGUGGACUUA	229	4143	ACUUGGACUUAUUAUUAAG	1880
4143	UGAUGAGUAUUAUUAAG	230	4143	UGAUGAGUAUUAUUAAG	230	4161	CGUGGUUAUUAUUAUUAAG	1881
4161	GUACCCUGGACAAAGGUAU	231	4161	GUACCCUGGACAAAGGUAU	231	4179	ACAUCCUUGUCCAGGUAU	1882
4179	UGCUGGUUAUUAUUAAG	232	4179	UGCUGGUUAUUAUUAAG	232	4197	CUCAAGUGUAUUAUUAAG	1883
4197	GGAAGCUAAGACUGCUCU	233	4197	GGAAGCUAAGACUGCUCU	233	4215	AAGAGCAGUUAUUAUUAAG	1884
4215	UAAGAAUUGCAUUAUUAAG	234	4215	UAAGAAUUGCAUUAUUAAG	234	4233	UGCAGAUUUGCAUUAUUAAG	1885
4233	AUUUAUUAUUAUUAAG	235	4233	AUUUAUUAUUAUUAAG	235	4251	UGAAGGUUAUUAUUAUUAAG	1886
4251	AGAAGCAGCUUAUUAAG	236	4251	AGAAGCAGCUUAUUAAG	236	4269	CUUAGCAUUAUUAUUAAG	1887
4269	GGAAGAGAUUAUUAAG	237	4269	GGAAGAGAUUAUUAAG	237	4287	AGUCCUUAUUAUUAUUAAG	1888
4287	UGAUUCCUGGAAUUAUUAAG	238	4287	UGAUUCCUGGAAUUAUUAAG	238	4305	UCUCAUUAUUAUUAUUAAG	1889
4305	AGAAUCCUGGAAUUAUUAAG	239	4305	AGAAUCCUGGAAUUAUUAAG	239	4323	AGCAUUAUUAUUAUUAAG	1890
4323	UGAAGAGACAAUUAUUAAG	240	4323	UGAAGAGACAAUUAUUAAG	240	4341	UAUUUUAUUAUUAUUAAG	1891
4341	AUUGCCUUAUUAUUAAG	241	4341	AUUGCCUUAUUAUUAAG	241	4359	AUCCAUUAUUAUUAUUAAG	1892
4359	UGUUAAGGACAAUUAUUAAG	242	4359	UGUUAAGGACAAUUAUUAAG	242	4377	UGCCAUUAUUAUUAUUAAG	1893
4377	AACCAUUAUUAUUAUUAAG	243	4377	AACCAUUAUUAUUAUUAAG	243	4395	UAACUUAUUAUUAUUAAG	1894
4395	UAAGGAAUUAUUAUUAAG	244	4395	UAAGGAAUUAUUAUUAAG	244	4413	UAAGAAUUAUUAUUAUUAAG	1895
4413	AGAGGGCAUUAUUAUUAAG	245	4413	AGAGGGCAUUAUUAUUAAG	245	4431	AUAGCAUUAUUAUUAUUAAG	1896
		246			246			1897

(400/110\_US)

4431	UGGUGUCCGAUUCUUCUU	247	4431	UGGUGUCCGAUUCUUCUU	247	4449	AAAGAAGAAUCCGACACCA	1898
4449	UUAUACUAGUAAAGAGCCU	248	4449	UUAUACUAGUAAAGAGCCU	248	4467	AGGCUUUUACUAGUAA	1899
4467	UGAGCUUCUUAUUAAGG	249	4467	UGAGCUUCUUAUUAAGG	249	4485	CGUAAUUAJAGAAUCUACA	1900
4485	GAAGCUAGAACUCUUAUU	250	4485	GAAGCUAGAACUCUUAUU	250	4503	AUUUAGAGAGUUCAGCUUC	1901
4503	UGAGCGCUUGUCACAAUG	251	4503	UGAGCGCUUGUCACAAUG	251	4521	CAUUGUGACAAAGCGGCUCA	1902
4521	GCCAAUUGGUUAUGGACA	252	4521	GCCAAUUGGUUAUGGACA	252	4539	UGUCAUAUAAACCAUUGGC	1903
4539	ACAUGGUUUUAUUAUGAA	253	4539	ACAUGGUUUUAUUAUGAA	253	4557	UCCAAGAUUAAACCAUGU	1904
4557	AGAGGUGCGCGCUUAUG	254	4557	AGAGGUGCGCGCUUAUG	254	4575	CAUACAGCGCGCAGCCUCU	1905
4575	GCGUUCUCUUAAGCUCUCU	255	4575	GCGUUCUCUUAAGCUCUCU	255	4593	AGGAGCUUUAAGAGAGAGCG	1906
4593	UGCGUAGUGUCAGUAUCA	256	4593	UGCGUAGUGUCAGUAUCA	256	4611	UGAUACUGACACUACGGCA	1907
4611	AUCACAGAGUGCUUAUCU	257	4611	AUCACAGAGUGCUUAUCU	257	4629	AGUACACAGCAUUGGUAU	1908
4629	UACAUUAUUGGAUACCU	258	4629	UACAUUAUUGGAUACCU	258	4647	GAGGUUCCAUUAUUAUGUA	1909
4647	CACUUCGUCUACAAAGACA	259	4647	CACUUCGUCUACAAAGACA	259	4665	UGUCUUUGAUGACGAAGUG	1910
4665	AUCGAGGAGCACUUUGUA	260	4665	AUCGAGGAGCACUUUGUA	260	4683	UACAAAGUGUCCUCUAGAU	1911
4683	AGAAACAGUUCUUGGCU	261	4683	AGAAACAGUUCUUGGCU	261	4701	AGCCAAAGAAACUCUUUCU	1912
4701	UGGCUUCUACAGAGAUUGG	262	4701	UGGCUUCUACAGAGAUUGG	262	4719	CCAAUCUCUGUAAAGAGCA	1913
4719	GUCCUUAUCAGGACGCGU	263	4719	GUCCUUAUCAGGACGCGU	263	4737	ACGUGUCCUGAAUAGGAC	1914
4737	UACAGAGUUAAGGUUGAA	264	4737	UACAGAGUUAAGGUUGAA	264	4755	UUAACACCUAACUCUUGUA	1915
4755	AUUUCUUAAGCGUGUGAC	265	4755	AUUUCUUAAGCGUGUGAC	265	4773	GUCACCAACGCUUAAGAAU	1916
4773	CAAAUUGUGUACCCACAU	266	4773	CAAAUUGUGUACCCACAU	266	4791	AGUGUGUACGACAAUUUUG	1917
4791	UCUGGAGAGCGCGUGGAG	267	4791	UCUGGAGAGCGCGUGGAG	267	4809	CUCGACGGGCGUCCUCAGA	1918
4809	GUUUCUUAAGCGGUGAG	268	4809	GUUUCUUAAGCGGUGAG	268	4827	CUCACGUAAGAUAAGAAC	1919
4827	GGUUCUUAAGCGGUGAG	269	4827	GGUUCUUAAGCGGUGAG	269	4845	UUUGUACGUGAAAGAAC	1920
4845	ACUAAAGAGUCUUAUCC	270	4845	ACUAAAGAGUCUUAUCC	270	4863	GGUAAAGAGACUCUUUAGU	1921
4863	CCUGCGGAGGUAAGACU	271	4863	CCUGCGGAGGUAAGACU	271	4881	AGUUAACCUCCCGCAGG	1922
4881	UAUAAAGUGUUAACACU	272	4881	UAUAAAGUGUUAACACU	272	4899	AGUUGAGAACACUUUUUA	1923
4899	UGUGGACACACUAUUCU	273	4899	UGUGGACACACUAUUCU	273	4917	GAGUUAUGUUGUCCACA	1924
4917	CCACACACAGCUUGUGAU	274	4917	CCACACACAGCUUGUGAU	274	4935	AUCCAAAGCUGUGUGUGG	1925
4935	UAUGUCUAUGACAUUGGA	275	4935	UAUGUCUAUGACAUUGGA	275	4953	UCCAUAUGUCAUAGACUA	1926
4953	ACAGCAGUUGGUCCAACA	276	4953	ACAGCAGUUGGUCCAACA	276	4971	UGUUGGACCAACUGGUGU	1927
4971	AUACUUGGAUGGUGUGAU	277	4971	AUACUUGGAUGGUGUGAU	277	4989	AUCAGCACCACUCCAAUGU	1928
4989	UGUUAACAAAUUAACCU	278	4989	UGUUAACAAAUUAACCU	278	5007	AGGUUAUUUUUUGUAACA	1929
5007	UCAUGUAAAUCAUGAGGU	279	5007	UCAUGUAAAUCAUGAGGU	279	5025	ACCCUAGUUAUUUACAUGA	1930
5025	UAAGACUUUCUUUGUACUA	280	5025	UAAGACUUUCUUUGUACUA	280	5043	UAGUACAAAGAAAGUCUUA	1931
5043	ACCUAGUGAUGACACACUA	281	5043	ACCUAGUGAUGACACACUA	281	5061	UAGUGUGUCAUCACUAGGU	1932
5061	ACGUAGUGAAGCUUUCGAG	282	5061	ACGUAGUGAAGCUUUCGAG	282	5079	CUCGAAAGCUUCACUACGU	1933
5079	GUACUACCAUACUCUUGAU	283	5079	GUACUACCAUACUCUUGAU	283	5097	AUCAAGAGUUGGUAGUAC	1934
5097	UGAGAGUUUUUGGUAGG	284	5097	UGAGAGUUUUUGGUAGG	284	5115	CCUACCAAGAAACUCUCA	1935
5115	GUACAGUCUGCUUUAAC	285	5115	GUACAGUCUGCUUUAAC	285	5133	GUUUAAGCAGACAUUGUAC	1936
5133	CCACAAAGAAUUGGAA	286	5133	CCACAAAGAAUUGGAA	286	5151	UUUCCAUUUUUUGUGUGG	1937
5151	AUUUCCUUAAGUUGGUGU	287	5151	AUUUCCUUAAGUUGGUGU	287	5169	ACCACCAUUGAGGAAAU	1938
5169	UUUAACUUAUUAUUAUGG	288	5169	UUUAACUUAUUAUUAUGG	288	5187	CCAUUUAAUUGAAGUUAUA	1939



(400/110\_US)

5187	GGCUGAUACAUAUUGUUAU	289	5187	GGCUGAUACAUAUUGUUAU	289	5205	AUAACAUAUUGUAUACAGCC	1940
5205	UUUGUCUAGUGUUUUUAUA	290	5205	UUUGUCUAGUGUUUUUAUA	290	5223	UAUAACAACAGUACAGCAA	1941
5223	AGCAUUAACAACAGCUUGAA	291	5223	AGCAUUAACAACAGCUUGAA	291	5241	UUAACAAGCUGUUAAGUGCU	1942
5241	AGUCAUAUUAUUAUUAUUA	292	5241	AGUCAUAUUAUUAUUAUUA	292	5259	UGGUGCAUUAUUAUUAUUA	1943
5259	AGCAUUAACAACAGCUUGAA	293	5259	AGCAUUAACAACAGCUUGAA	293	5277	AUAAGCCUUAUUAUUAUUA	1944
5277	UUAUAGAGCCCGUGUGUGU	294	5277	UUAUAGAGCCCGUGUGUGU	294	5295	ACCAAGCUGUUAUUAUUA	1945
5295	UGAUGUGCUUAUUAUUAUUA	295	5295	UGAUGUGCUUAUUAUUAUUA	295	5313	ACAAAGUUAUUAUUAUUA	1946
5313	UGCAUUAACAACAGCUUGAA	296	5313	UGCAUUAACAACAGCUUGAA	296	5331	GUAAAGCUGUUAUUAUUA	1947
5331	CAGUAUAUAUAUUAUUAUUA	297	5331	CAGUAUAUAUAUUAUUAUUA	297	5349	GCCAACAGUUAUUAUUAUUA	1948
5349	CGAGCUUGUGUAUUAUUAUUA	298	5349	CGAGCUUGUGUAUUAUUAUUA	298	5367	UCUGACAUUAUUAUUAUUA	1949
5367	AGAAACUAUUAUUAUUAUUA	299	5367	AGAAACUAUUAUUAUUAUUA	299	5385	AAGUUGGCUUAUUAUUAUUA	1950
5385	UCUACAGCAUUAUUAUUAUUA	300	5385	UCUACAGCAUUAUUAUUAUUA	300	5403	CAAUUAUUAUUAUUAUUA	1951
5403	GGAUUAUUAUUAUUAUUAUUA	301	5403	GGAUUAUUAUUAUUAUUAUUA	301	5421	AACUGCUUAUUAUUAUUA	1952
5421	UCUUAUUAUUAUUAUUAUUA	302	5421	UCUUAUUAUUAUUAUUAUUA	302	5439	UUAUUAUUAUUAUUAUUA	1953
5439	ACAUUAUUAUUAUUAUUAUUA	303	5439	ACAUUAUUAUUAUUAUUAUUA	303	5457	AGUUUUGUUAUUAUUAUUA	1954
5457	UACUUAUUAUUAUUAUUAUUA	304	5457	UACUUAUUAUUAUUAUUAUUA	304	5475	UACACCCGUAUUAUUAUUA	1955
5475	AGAAGCUGUAUUAUUAUUAUUA	305	5475	AGAAGCUGUAUUAUUAUUAUUA	305	5493	CAUAUUAUUAUUAUUAUUA	1956
5493	GGUUAUUAUUAUUAUUAUUAUUA	306	5493	GGUUAUUAUUAUUAUUAUUAUUA	306	5511	AUCAUUAUUAUUAUUAUUA	1957
5511	UUAUUAUUAUUAUUAUUAUUA	307	5511	UUAUUAUUAUUAUUAUUAUUA	307	5529	AACACCUUAUUAUUAUUA	1958
5529	UUAUUAUUAUUAUUAUUAUUA	308	5529	UUAUUAUUAUUAUUAUUAUUA	308	5547	ACACAUAUUAUUAUUAUUA	1959
5547	UGGUGUGUAUUAUUAUUAUUA	309	5547	UGGUGUGUAUUAUUAUUAUUA	309	5565	UUGUGUAUUAUUAUUAUUA	1960
5565	AUAUUAUUAUUAUUAUUAUUA	310	5565	AUAUUAUUAUUAUUAUUAUUA	310	5583	CUCUUAUUAUUAUUAUUA	1961
5583	GUCUUAUUAUUAUUAUUAUUA	311	5583	GUCUUAUUAUUAUUAUUAUUA	311	5601	CAUCAUUAUUAUUAUUAUUA	1962
5601	GUCUGCAUUAUUAUUAUUAUUA	312	5601	GUCUGCAUUAUUAUUAUUAUUA	312	5619	CUCAGCAGUUAUUAUUAUUA	1963
5619	GUUAUUAUUAUUAUUAUUAUUA	313	5619	GUUAUUAUUAUUAUUAUUAUUA	313	5637	ACCUUAUUAUUAUUAUUAUUA	1964
5637	UUAUUAUUAUUAUUAUUAUUA	314	5637	UUAUUAUUAUUAUUAUUAUUA	314	5655	AUUCGCAUUAUUAUUAUUA	1965
5655	UGAGUUAUUAUUAUUAUUAUUA	315	5655	UGAGUUAUUAUUAUUAUUAUUA	315	5673	AUAUUAUUAUUAUUAUUAUUA	1966
5673	UCAGUGUGUAUUAUUAUUAUUA	316	5673	UCAGUGUGUAUUAUUAUUAUUA	316	5691	AGUGUAUUAUUAUUAUUAUUA	1967
5691	UUAUUAUUAUUAUUAUUAUUA	317	5691	UUAUUAUUAUUAUUAUUAUUA	317	5709	CUCUUAUUAUUAUUAUUAUUA	1968
5709	GACCCUUAUUAUUAUUAUUAUUA	318	5709	GACCCUUAUUAUUAUUAUUAUUA	318	5727	GUCAUUAUUAUUAUUAUUAUUA	1969
5727	CGGAGCUUAUUAUUAUUAUUA	319	5727	CGGAGCUUAUUAUUAUUAUUA	319	5745	CUUUAUUAUUAUUAUUAUUA	1970
5745	GAUGUCAGUAUUAUUAUUAUUA	320	5745	GAUGUCAGUAUUAUUAUUAUUA	320	5763	UCCUUAUUAUUAUUAUUAUUA	1971
5763	ACCAUUAUUAUUAUUAUUAUUA	321	5763	ACCAUUAUUAUUAUUAUUAUUA	321	5781	GAUAUUAUUAUUAUUAUUAUUA	1972
5781	CUACAAGGAUUAUUAUUAUUAUUA	322	5781	CUACAAGGAUUAUUAUUAUUAUUA	322	5799	GUAGAUGUUAUUAUUAUUAUUA	1973
5799	CACUAUUAUUAUUAUUAUUAUUA	323	5799	CACUAUUAUUAUUAUUAUUAUUA	323	5817	AGGCUUAUUAUUAUUAUUAUUA	1974
5817	UGUGUGUAUUAUUAUUAUUAUUA	324	5817	UGUGUGUAUUAUUAUUAUUAUUA	324	5835	AUGGUAUUAUUAUUAUUAUUA	1975
5835	UGGAGUUAUUAUUAUUAUUAUUA	325	5835	UGGAGUUAUUAUUAUUAUUAUUA	325	5853	CUCUGUAUUAUUAUUAUUAUUA	1976
5853	GAUUAUUAUUAUUAUUAUUAUUA	326	5853	GAUUAUUAUUAUUAUUAUUAUUA	326	5871	AUCCAUUAUUAUUAUUAUUAUUA	1977
5871	UGGUAUUAUUAUUAUUAUUAUUA	327	5871	UGGUAUUAUUAUUAUUAUUAUUA	327	5889	AUCCUUAUUAUUAUUAUUAUUA	1978
5889	UUAUUAUUAUUAUUAUUAUUAUUA	328	5889	UUAUUAUUAUUAUUAUUAUUAUUA	328	5907	CUCUGUAUUAUUAUUAUUAUUA	1979
5907	GCAGCUUAUUAUUAUUAUUAUUA	329	5907	GCAGCUUAUUAUUAUUAUUAUUA	329	5925	UACAAGGCUUAUUAUUAUUAUUA	1980
5925	ACCAUUAUUAUUAUUAUUAUUAUUA	330	5925	ACCAUUAUUAUUAUUAUUAUUAUUA	330	5943	UGGUAUUAUUAUUAUUAUUAUUA	1981

(400/110\_US)

5943	AAUUGCGAGUUUUGAUAAU	331	5943	AAUUGCGAGUUUUGAUAAU	331	5961	AUUUCAAACAAUCGCAUUU	1982
5961	UUUCAAACUCACAUUUCU	332	5961	UUUCAAACUCACAUUUCU	332	5979	AGAACAUUGAGUUUGAAA	1983
5979	UACACAAAUUUGCUGAU	333	5979	UACACAAAUUUGCUGAU	333	5997	AUCAGCAAUUUGUGUUUA	1984
5997	UGAUUAAAUUCAAUAGACA	334	5997	UGAUUAAAUUCAAUAGACA	334	6015	UGUAAUUUGAUUUAAAUCA	1985
6015	AGGUUACAAAGCCAGCU	335	6015	AGGUUACAAAGCCAGCU	335	6033	AGUGGCUUUGUGAAGCCU	1986
6033	UUCACGAGAGCUAUCUGC	336	6033	UUCACGAGAGCUAUCUGC	336	6051	GACAGUAGCCGUAUGGAA	1987
6051	CACAUUCUCCAGACUUG	337	6051	CACAUUCUCCAGACUUG	337	6069	CAAGUCUGGGAAGAAUGUG	1988
6069	GAUUGCGAUUGAGUGGU	338	6069	GAUUGCGAUUGAGUGGU	338	6087	AGCACUACUAGCCAUUC	1989
6087	UAUUGACUAUAGACAUUA	339	6087	UAUUGACUAUAGACAUUA	339	6105	AUAGUGCUAUAGUCAUA	1990
6105	UUCAGCGAGUUUCAAAGAA	340	6105	UUCAGCGAGUUUCAAAGAA	340	6123	UUUUGGAAACUCGUGAA	1991
6123	AGGUGCUAAAUUACUGCAU	341	6123	AGGUGCUAAAUUACUGCAU	341	6141	AUGCAGUAUUUAGGACCU	1992
6141	UAAGCCAAUUGUUGGCAC	342	6141	UAAGCCAAUUGUUGGCAC	342	6159	GUGCCAAACAAUUGGCUUA	1993
6159	CAUUAACCCAGGCUAACCC	343	6159	CAUUAACCCAGGCUAACCC	343	6177	GGUUGUAGCCUGGUUUAUG	1994
6177	CAAGACAACGUUCAAACCA	344	6177	CAAGACAACGUUCAAACCA	344	6195	UGGUUUGAACGUGUUGUUG	1995
6195	AAACACUUGGUGUUAACGU	345	6195	AAACACUUGGUGUUAACGU	345	6213	ACGUAAACACCAAGUGUUU	1996
6213	UUGUCUUUGGAGUACAAAG	346	6213	UUGUCUUUGGAGUACAAAG	346	6231	CUUUGUACUCCAAAGACAA	1997
6231	GCCAGUAGAUUUAUUAUUA	347	6231	GCCAGUAGAUUUAUUAUUA	347	6249	AUUUGAGUAUCUACUGGC	1998
6249	UUCAUUUGAAGUUCUGGCA	348	6249	UUCAUUUGAAGUUCUGGCA	348	6267	UGCCAGAACUUAUUAUUA	1999
6267	AGUAGAAGACACACAAGGA	349	6267	AGUAGAAGACACACAAGGA	349	6285	UCCUUGUGUGUUCUUCU	2000
6285	AAUGGACAACUUCUGUUGU	350	6285	AAUGGACAACUUCUGUUGU	350	6303	CAAGACAAGAUUGUCCAUU	2001
6303	UGAAGUCUACCAACCCACC	351	6303	UGAAGUCUACCAACCCACC	351	6321	GGUGGUUGUUGACUUUA	2002
6321	CUCUGAAGAAUAGUGGAA	352	6321	CUCUGAAGAAUAGUGGAA	352	6339	UCCACUACUUCUUCAGAG	2003
6339	AAUCCUACCAUACAGAG	353	6339	AAUCCUACCAUACAGAG	353	6357	CUUCUGUAGUGGAGGUUU	2004
6357	GGAAGUACUAGUGUGAC	354	6357	GGAAGUACUAGUGUGAC	354	6375	GACACUACUAGAUUCC	2005
6375	CGUGAAACUACCGAAGUU	355	6375	CGUGAAACUACCGAAGUU	355	6393	AACUUGGUAUUGUUCACG	2006
6393	UUAAGCAUAGUACUUAU	356	6393	UUAAGCAUAGUACUUAU	356	6411	AAGUAGCAUUGCCUACA	2007
6411	UAAACCAUACAGUAGAGGU	357	6411	UAAACCAUACAGUAGAGGU	357	6429	ACCUACUUGUAGUGUUA	2008
6429	UGUAAAGUAACACAAGAG	358	6429	UGUAAAGUAACACAAGAG	358	6447	CUCUUGUUAUUAUUA	2009
6447	GUUAGGUCAUGAGGAGUUA	359	6447	GUUAGGUCAUGAGGAGUUA	359	6465	AAGUCCUACUAGCCUAAAC	2010
6465	UAUGGCUUUAUGUGGAA	360	6465	UAUGGCUUUAUGUGGAA	360	6483	UUCACAUAAAGCAGCCAU	2011
6483	AAACACAAGCAUUAUUAU	361	6483	AAACACAAGCAUUAUUAU	361	6501	AUUGGUAUUGUUGUUA	2012
6501	UAAGAAACCUAAUAGGCUU	362	6501	UAAGAAACCUAAUAGGCUU	362	6519	AAGCUCAUUAUUGUUA	2013
6519	UUCACUAGCCUUAUUAUUA	363	6519	UUCACUAGCCUUAUUAUUA	363	6537	UAAACUUAAGGCUAGUAA	2014
6537	AAACACAUUGCCACUUAU	364	6537	AAACACAUUGCCACUUAU	364	6555	UAGAGUGGCAUUAUUA	2015
6555	UGGUUUGGCUUUAUUAUUA	365	6555	UGGUUUGGCUUUAUUAUUA	365	6573	AUUAUUGGCAUUAUUA	2016
6573	UAGUUGUCCUUGGAGUAAA	366	6573	UAGUUGUCCUUGGAGUAAA	366	6591	UUUACUCCAAAGGAACUA	2017
6591	AUUUUGGCUUUAUUAUUA	367	6591	AUUUUGGCUUUAUUAUUA	367	6609	UUUGACAUAAAGCCAAAUU	2018
6609	ACCAUUCUUAAGGACAAGCA	368	6609	ACCAUUCUUAAGGACAAGCA	368	6627	UUCUUGUCCUUAAGAAUUG	2019
6627	AGCAUUAACACAUAUUAU	369	6627	AGCAUUAACACAUAUUAU	369	6645	AUUUGUUGUUAUUAUUG	2020
6645	UUGGCUUAAGGAGUUAUUA	370	6645	UUGGCUUAAGGAGUUAUUA	370	6663	UGCUAAUUCUUAAGCGAA	2021
6663	ACAACGUGUUAUUAUUAU	371	6663	ACAACGUGUUAUUAUUAU	371	6681	AUUGUAAACACACGUGU	2022
6681	UUUAUUGCCUUAUUGUUAU	372	6681	UUUAUUGCCUUAUUGUUAU	372	6699	AAACACAUAAGGCAUUA	2023

(400/110\_US)

6699	UACAUUUAUUGUCCAAUUG	373	6699	UACAUUUAUUGUCCAAUUG	373	6717	CAUUUGGAACAAUUAUUGUA	2024
6717	GUGUACUUUUUACUAAAAGU	374	6717	GUGUACUUUUUACUAAAAGU	374	6735	ACUUUUUAGUAAAAGUACAC	2025
6735	UACCAUUUCUAGAAUUAAGA	375	6735	UACCAUUUCUAGAAUUAAGA	375	6753	UGUAAUUUCUAGAAUUGGUA	2026
6753	AGCUUACUACCUACAACU	376	6753	AGCUUACUACCUACAACU	376	6771	AGUUGUAGGUAGUGAAGCU	2027
6771	UAUUGCUAAAUAUAGUGU	377	6771	UAUUGCUAAAUAUAGUGU	377	6789	AACACUUAUUUUAAGCAUAU	2028
6789	UAAGAGUGUUGCUAAUUA	378	6789	UAAGAGUGUUGCUAAUUA	378	6807	UAUUUAGCAACACUUAU	2029
6807	AUGUUUGGAGUCCGGCAU	379	6807	AUGUUUGGAGUCCGGCAU	379	6825	UAUGCGGCAUCCAAACAU	2030
6825	UAUUUUGUAGUAGUACCC	380	6825	UAUUUUGUAGUAGUACCC	380	6843	GGUGGACUUCACAUUAUA	2031
6843	CAAAUUUUCUAAAUGUUC	381	6843	CAAAUUUUCUAAAUGUUC	381	6861	GAACAAUUUJAGAAAUIUG	2032
6861	CACAACCGCUAUGUGGCUA	382	6861	CACAACCGCUAUGUGGCUA	382	6879	UAGCCACAUJAGCGAUUGUG	2033
6879	AUUGUUGUUAAGUAUUGC	383	6879	AUUGUUGUUAAGUAUUGC	383	6897	GCAAAUUCUUAACAACAAU	2034
6897	CUUAGGUUCUUAUCUGU	384	6897	CUUAGGUUCUUAUCUGU	384	6915	ACAGAUUJAGAGAACCUAAG	2035
6915	UGUACUGUCGCUUUUGGU	385	6915	UGUACUGUCGCUUUUGGU	385	6933	ACAAAAGCAGCGAUUA	2036
6933	UGUACUGUCGCUUUUGGU	386	6933	UGUACUGUCGCUUUUGGU	386	6951	AAAUAJAGAUAGAGUACA	2037
6951	UGGUGGCUUCUUAUUGU	387	6951	UGGUGGCUUCUUAUUGU	387	6969	ACAAUAGAGAGAGACCA	2038
6969	UAAUGGCGUUAAGAAUUG	388	6969	UAAUGGCGUUAAGAAUUG	388	6987	CAAUUCUUAACGCCAUUA	2039
6987	GUUCUUAUUCGCUAAC	389	6987	GUUCUUAUUCGCUAAC	389	7005	GUUAAGCGAAUUAAGAUAC	2040
7005	CGUUAACUACUAGGAUUC	390	7005	CGUUAACUACUAGGAUUC	390	7023	GAAUCCAUJAGUAGUACG	2041
7023	CUUGAAGGUUCUUAUUGU	391	7023	CUUGAAGGUUCUUAUUGU	391	7041	AGGAAAGAACCUUCACAG	2042
7041	UUGCAGCAUUGUUAAGU	392	7041	UUGCAGCAUUGUUAAGU	392	7059	ACUUAACAACUUGUGCAA	2043
7059	UGGAUUAAGUCCUUGAU	393	7059	UGGAUUAAGUCCUUGAU	393	7077	AUCAAGGAGUCUUAUCCA	2044
7077	UUCUUAUCCAGCUUGAA	394	7077	UUCUUAUCCAGCUUGAA	394	7095	UUAAGAGCGUGGAUAGAA	2045
7095	AACCAUACAGGUGAGAU	395	7095	AACCAUACAGGUGAGAU	395	7113	AUCUGCACCGUAAUGGU	2046
7113	UUCUUGCUAAGCUAGAC	396	7113	UUCUUGCUAAGCUAGAC	396	7131	GUCUGCUUUGUACGAUAA	2047
7131	CUUGACAAUUUJAGGUGU	397	7131	CUUGACAAUUUJAGGUGU	397	7149	CAGACUUAUUUJUGCAAG	2048
7149	GGCCGUGAGUGGUGUUG	398	7149	GGCCGUGAGUGGUGUUG	398	7167	CAAAUCCACUACGCGGCC	2049
7167	GGCAUUAUUGUUGUACAC	399	7167	GGCAUUAUUGUUGUACAC	399	7185	UGUGAACACAUUAUUGCC	2050
7185	AAAAUUCUUUAUUUAUA	400	7185	AAAAUUCUUUAUUUAUA	400	7203	UAAUAAUUAUAAAGAUUUU	2051
7203	AGGUCUUUCAGCUAAUUG	401	7203	AGGUCUUUCAGCUAAUUG	401	7221	CAUUAUAGCUGAAAGACCU	2052
7221	GCAGGUGUUCUUGGCUAU	402	7221	GCAGGUGUUCUUGGCUAU	402	7239	AUAGCCAAAGAACACCGUC	2053
7239	UUUUGCUAGCUUUUAUC	403	7239	UUUUGCUAGCUUUUAUC	403	7257	GAUGAAUUGACUAGCAAAA	2054
7257	CAGCAUUCUUGGCUAUG	404	7257	CAGCAUUCUUGGCUAUG	404	7275	CAUGAGCAAGAAUUGCUG	2055
7275	GUGGUUUAUUAUUAUUA	405	7275	GUGGUUUAUUAUUAUUA	405	7293	AUAUUAUUAUUAUUAUUA	2056
7293	UGUACAAUUGGACCCGUU	406	7293	UGUACAAUUGGACCCGUU	406	7311	AACGGUGGCUUUAUUAUA	2057
7311	UUCUGCAUUGUUAAGAU	407	7311	UUCUGCAUUGUUAAGAU	407	7329	CAUCCUAAUUAUUAUUA	2058
7329	GUACAUUCUUCUUGCUUCU	408	7329	GUACAUUCUUCUUGCUUCU	408	7347	AGAAGAAAGAAUUAUUA	2059
7347	UUUCUACUACAUUAAGG	409	7347	UUUCUACUACAUUAAGG	409	7365	CUUCCAUUAUUAUUAUUA	2060
7365	GAGCUAUGUUAUUAUUA	410	7365	GAGCUAUGUUAUUAUUA	410	7383	CAUGAAUUAUUAUUAUUA	2061
7383	GGAUGUUGCACCUUUCG	411	7383	GGAUGUUGCACCUUUCG	411	7401	CGAUGAGGUGCAACCAUCC	2062
7401	GACUUGCAUUAUUAUUA	412	7401	GACUUGCAUUAUUAUUA	412	7419	AUAGCAUUAUUAUUAUUA	2063
7419	UAAGCGCAUUCGUGCCACA	413	7419	UAAGCGCAUUCGUGCCACA	413	7437	UGUGGCACGAUUAUUAUUA	2064
7437	ACGGUUGAGUGUACAAU	414	7437	ACGGUUGAGUGUACAAU	414	7455	AGUUGUACACUACCAACGCGU	2065



(400/110\_US)

7455	UAUUGUUAUUGGCAUAG	415	7455	UAUUGUUAUUGGCAUAG	415	7473	CUUCAUGCCAUUAACAUA	2066
7473	GAGAUUUUUAUUGUUAU	416	7473	GAGAUUUUUAUUGUUAU	416	7491	AUAGACAUAGAAAGAUUC	2067
7491	UGCAAUUGGAGCGCGGC	417	7491	UGCAAUUGGAGCGCGGC	417	7509	GCACGGCCUUAUUGCA	2068
7509	CUUCUGCAAGACACAAU	418	7509	CUUCUGCAAGACACAAU	418	7527	AUUGAGUUCUUGCAGAAG	2069
7527	UUGGAAUUGUCUUAUUG	419	7527	UUGGAAUUGUCUUAUUG	419	7545	ACAAUUGAGACAAUUGCAA	2070
7545	UGACACAUUUGCAGUUG	420	7545	UGACACAUUUGCAGUUG	420	7563	ACCAGUGCAAAUUGUGUA	2071
7563	UAGUACAUUUAUUGAU	421	7563	UAGUACAUUUAUUGAU	421	7581	AUCACUAAUAGAAUUGUA	2072
7581	UGAAGUUGUCUGAUUUG	422	7581	UGAAGUUGUCUGAUUUG	422	7599	CAUACACGAGCAACUUA	2073
7599	GUCACUCCAGUUAUAGA	423	7599	GUCACUCCAGUUAUAGA	423	7617	CUUUAUAAACUGGAGUG	2074
7617	ACCAUACCCUACUGAC	424	7617	ACCAUACCCUACUGAC	424	7635	GUCAGUAGGUUUAUUGU	2075
7635	CCAGUACUAGUUAUUGU	425	7635	CCAGUACUAGUUAUUGU	425	7653	AACAUAUACGAGUAGUG	2076
7653	UGAUGUUGUUGUGUAAA	426	7653	UGAUGUUGUUGUGUAAA	426	7671	UUUCACAGCAACACUUA	2077
7671	AAUUGGCGGCUUACCCUC	427	7671	AAUUGGCGGCUUACCCUC	427	7689	GAGGUAAGCGCGCCAUUU	2078
7689	CUACUUAUAGAAAGGUGU	428	7689	CUACUUAUAGAAAGGUGU	428	7707	ACCAGCCUUGUCAAAGUAG	2079
7707	UCAAAGACCUUAGAGAGA	429	7707	UCAAAGACCUUAGAGAGA	429	7725	UCUCUAUAGGUUUUUGA	2080
7725	ACAUCGCGUCCCAUUUU	430	7725	ACAUCGCGUCCCAUUUU	430	7743	AAAUUGGAGAGCGGAUGU	2081
7743	UGUCAAUUUAGCAAUUUG	431	7743	UGUCAAUUUAGCAAUUUG	431	7761	CAAUUUGUCAAUUGACA	2082
7761	GAGAGCUAACACACUAAA	432	7761	GAGAGCUAACACACUAAA	432	7779	UUUAGUUGUUAAGCUCUC	2083
7779	AGGUUACUGCCUUAUUAU	433	7779	AGGUUACUGCCUUAUUAU	433	7797	AUUAUAGCGAGUGAACC	2084
7797	UGUCAUAGUUAUUGAGGC	434	7797	UGUCAUAGUUAUUGAGGC	434	7815	GCAUCAAAACUUAUGACA	2085
7815	CAAGUCCAAUUGCGACGAG	435	7815	CAAGUCCAAUUGCGACGAG	435	7833	CUCGUCGCAUUGGACUUG	2086
7833	GUCUGCUUAUAGUUGCU	436	7833	GUCUGCUUAUAGUUGCU	436	7851	AGCAGACUUAAGAGCAGAC	2087
7851	UUCUGUGUACUACAGUCAG	437	7851	UUCUGUGUACUACAGUCAG	437	7869	CUGACUGUAGUACACAGAA	2088
7869	GCUGAUGUCCCAACCUAU	438	7869	GCUGAUGUCCCAACCUAU	438	7887	AUAAGGUUGGCAUUCAGC	2089
7887	UCUGUUGCUUAGCCAGCU	439	7887	UCUGUUGCUUAGCCAGCU	439	7905	AGCUUGGUCAAGCAACAGA	2090
7905	AGUAGUACUGAAGUUGGA	440	7905	AGUAGUACUGAAGUUGGA	440	7923	UCCAACGUCUGUAACAAGA	2091
7923	CGUUAAGUUAUUGUUGCC	441	7923	CGUUAAGUUAUUGUUGCC	441	7941	GGAAACUUCAGUACUUAUCU	2092
7941	UUAUGUGCAGACCUUUAU	442	7941	UUAUGUGCAGACCUUUAU	442	7959	AGCAUCAAACAUUUAACG	2093
7959	UUAUGUGCAGACCUUUAU	443	7959	UUAUGUGCAGACCUUUAU	443	7977	UGAAAGGUGUGCAGACUAA	2094
7977	AGCAACUUAUAGUUGCCU	444	7977	AGCAACUUAUAGUUGCCU	444	7995	AGAAACACUAAAGUUGCU	2095
7995	UAUGGAAACUUAAGGCA	445	7995	UAUGGAAACUUAAGGCA	445	8013	UGCCUUAAGUUAUUGCAUA	2096
8013	ACUUGUUGCUACAGCUCAC	446	8013	ACUUGUUGCUACAGCUCAC	446	8031	GUGAGCUGUAGCAACAAGU	2097
8031	CAGCGAGUUAAGAAAGGU	447	8031	CAGCGAGUUAAGAAAGGU	447	8049	ACCCUUGCUAAACUGCGUG	2098
8049	UGUAGCUUAUAGUUGGUC	448	8049	UGUAGCUUAUAGUUGGUC	448	8067	GACACCAUUAAGGUAAGG	2099
8067	CCUUCUACAUUCGUGUA	449	8067	CCUUCUACAUUCGUGUA	449	8085	UGACACGAAUUGAAGAAAG	2100
8085	AGCUGCCCGACAAAGGUU	450	8085	AGCUGCCCGACAAAGGUU	450	8103	AACACCUUGUGCGGCAAGU	2101
8103	UGUUGAUCCGAGUUGAC	451	8103	UGUUGAUCCGAGUUGAC	451	8121	GUCACACUUGGUAACAACA	2102
8121	CACAAAGGAUUAUUGAA	452	8121	CACAAAGGAUUAUUGAA	452	8139	UUAUAUAACAUCCUUGUG	2103
8139	AUGUCUCAAACUUAUACAU	453	8139	AUGUCUCAAACUUAUACAU	453	8157	AUGUAAAGUUAUUGAGACAU	2104
8157	UCACUCUGACUUAAGAGUG	454	8157	UCACUCUGACUUAAGAGUG	454	8175	CACUUCUAAGUCAGAGUGA	2105
8175	GACAGGUGACAGUUGUAAC	455	8175	GACAGGUGACAGUUGUAAC	455	8193	GUUACACUUGCACCUGUC	2106
8193	CAAUUUCAUGCUCACCUAU	456	8193	CAAUUUCAUGCUCACCUAU	456	8211	AUAGGUGAGCAUGAAUUG	2107

(400/110\_US)

8211	UAAUAGGUAUUAUUA	457	8211	UAAUAGGUAUUAUUA	457	8229	CAUGUUUUAACCUUAUUA	2108
8229	GACGCCAGAGAUUUGGC	458	8229	GACGCCAGAGAUUUGGC	458	8247	GCCAAUGUCUGGCGUC	2109
8247	CGCAUUAUUGACUUAU	459	8247	CGCAUUAUUGACUUAU	459	8265	AUACAGUAUUAUUAUUA	2110
8265	UGCAAGGUAUUAUUAU	460	8265	UGCAAGGUAUUAUUAU	460	8283	GGCAUUAUUGCUUUGCA	2111
8283	CCAAGUAGCAUUAUUA	461	8283	CCAAGUAGCAUUAUUA	461	8301	GUGCAUUAUUGCUUUGG	2112
8301	CAUUAUUAUUAUUAU	462	8301	CAUUAUUAUUAUUAU	462	8319	CCAGAUUAGUAAACAUUG	2113
8319	GAUUAUUAUUAUUAU	463	8319	GAUUAUUAUUAUUAU	463	8337	CAUGUAGUCUUUAUUAU	2114
8337	GUCUUAUUAUUAUUA	464	8337	GUCUUAUUAUUAUUA	464	8355	CAGCUGUACAGUAAAGAC	2115
8355	GCGUAAACAAUUAUUA	465	8355	GCGUAAACAAUUAUUA	465	8373	ACUACGAUUAUUGUUAU	2116
8373	UGUGGCAAGAAACAAU	466	8373	UGUGGCAAGAAACAAU	466	8391	GUUUAUUAUUGGCGCA	2117
8391	CAUACCUUUAUUAUUA	467	8391	CAUACCUUUAUUAUUA	467	8409	AGUUAUUAUUAUUAU	2118
8409	UUGUGCAACUUAUUAU	468	8409	UUGUGCAACUUAUUAU	468	8427	CUGCUAGUUAUUAUUA	2119
8427	GGUUGCAUUAUUAUUA	469	8427	GGUUGCAUUAUUAUUA	469	8445	AGUUAUUAUUAUUAU	2120
8445	UACUAAAUUAUUAUUA	470	8445	UACUAAAUUAUUAUUA	470	8463	CUUGAGUGAUUAUUAU	2121
8463	GGUGGUAUUAUUAUUA	471	8463	GGUGGUAUUAUUAUUA	471	8481	CUUAGAGAUUAUUAUUA	2122
8481	UACUUAUUAUUAUUAU	472	8481	UACUUAUUAUUAUUAU	472	8499	CAUUAUUAUUAUUAUUA	2123
8499	GCUUAAGGCAUUAUUA	473	8499	GCUUAAGGCAUUAUUA	473	8517	CAUUAUUAUUAUUAUUA	2124
8517	GUGGUAUUAUUAUUAU	474	8517	GUGGUAUUAUUAUUAU	474	8535	CAUUAUUAUUAUUAUUA	2125
8535	GGUUGUAUUAUUAUUA	475	8535	GGUUGUAUUAUUAUUA	475	8553	CAUUAUUAUUAUUAUUA	2126
8553	GCGUUAUUAUUAUUAU	476	8553	GCGUUAUUAUUAUUAU	476	8571	UGACAUGAUUAUUAUUA	2127
8571	AUUAUUAUUAUUAUUA	477	8571	AUUAUUAUUAUUAUUA	477	8589	UGUUAUUAUUAUUAUUA	2128
8589	AAUUAUUAUUAUUAUUA	478	8589	AAUUAUUAUUAUUAUUA	478	8607	GUAAUUAUUAUUAUUA	2129
8607	CAAAGCAUUAUUAUUA	479	8607	CAAAGCAUUAUUAUUA	479	8625	ACUUAUUAUUAUUAUUA	2130
8625	UUGUUAUUAUUAUUAU	480	8625	UUGUUAUUAUUAUUAU	480	8643	AUUAUUAUUAUUAUUA	2131
8643	UUCUUAUUAUUAUUAU	481	8643	UUCUUAUUAUUAUUAU	481	8661	AAUUAUUAUUAUUAUUA	2132
8661	UGCAUUAUUAUUAUUA	482	8661	UGCAUUAUUAUUAUUA	482	8679	ACCAGUUAUUAUUAUUA	2133
8679	UUUUAUUAUUAUUAUUA	483	8679	UUUUAUUAUUAUUAUUA	483	8697	GCUAAUUAUUAUUAUUA	2134
8697	CCAGUUAUUAUUAUUA	484	8697	CCAGUUAUUAUUAUUA	484	8715	GUUAUUAUUAUUAUUA	2135
8715	CAUUAUUAUUAUUAUUA	485	8715	CAUUAUUAUUAUUAUUA	485	8733	GCAGUUAUUAUUAUUA	2136
8733	CCUUAUUAUUAUUAUUA	486	8733	CCUUAUUAUUAUUAUUA	486	8751	GAUUAUUAUUAUUAUUA	2137
8751	CAUUAUUAUUAUUAUUA	487	8751	CAUUAUUAUUAUUAUUA	487	8769	ACCAUUAUUAUUAUUA	2138
8769	UUUAUUAUUAUUAUUA	488	8769	UUUAUUAUUAUUAUUA	488	8787	UAAGCAUUAUUAUUAUUA	2139
8787	ACCGUUAUUAUUAUUA	489	8787	ACCGUUAUUAUUAUUA	489	8805	UCUUAUUAUUAUUAUUA	2140
8805	AGCAUUAUUAUUAUUA	490	8805	AGCAUUAUUAUUAUUA	490	8823	GAAGUUAUUAUUAUUA	2141
8823	CUUUAUUAUUAUUAUUA	491	8823	CUUUAUUAUUAUUAUUA	491	8841	ACGAGUUAUUAUUAUUA	2142
8841	UGUUAUUAUUAUUAUUA	492	8841	UGUUAUUAUUAUUAUUA	492	8859	GCCAAUUAUUAUUAUUA	2143
8859	CAUUAUUAUUAUUAUUA	493	8859	CAUUAUUAUUAUUAUUA	493	8877	AGGUUAUUAUUAUUAUUA	2144
8877	UUAUUAUUAUUAUUAUUA	494	8877	UUAUUAUUAUUAUUAUUA	494	8895	AUUAUUAUUAUUAUUA	2145
8895	UUAUUAUUAUUAUUAUUA	495	8895	UUAUUAUUAUUAUUAUUA	495	8913	AGAGUUAUUAUUAUUA	2146
8913	UGUUAUUAUUAUUAUUA	496	8913	UGUUAUUAUUAUUAUUA	496	8931	AGCAGUUAUUAUUAUUA	2147
8931	UGUUAUUAUUAUUAUUA	497	8931	UGUUAUUAUUAUUAUUA	497	8949	CUUUAUUAUUAUUAUUA	2148
8949	GGAUUAUUAUUAUUAUUA	498	8949	GGAUUAUUAUUAUUAUUA	498	8967	AGGUUAUUAUUAUUAUUA	2149

(400/110\_US)

8967	UGUGCCAUUUUUUAGAC	499	8967	UGUGCCAUUUUUUAGAC	499	8985	GUCAUAAUUAUUGGCACA	2150
8985	CACUAAUUUGUAGAGGGU	500	8985	CACUAAUUUGUAGAGGGU	500	9003	ACCCUAGCAAAUUAUG	2151
9003	UUCUAAUUUUUAUAGUGAG	501	9003	UUCUAAUUUUUAUAGUGAG	501	9021	CUCACUUAAGAAUAGAA	2152
9021	GCUCUGUCCAGACACUCGU	502	9021	GCUCUGUCCAGACACUCGU	502	9039	ACGAGUGUGGAGCGAAGC	2153
9039	UUAUGUGCUUAUGGAUGGU	503	9039	UUAUGUGCUUAUGGAUGGU	503	9057	ACGAUCAAUAGCACAUA	2154
9057	UUCUACUACUUAUUCU	504	9057	UUCUACUACUUAUUCU	504	9075	AGGAACUGUAUGAUGGAA	2155
9075	UAACACUACUAGGAGGGU	505	9075	UAACACUACUAGGAGGGU	505	9093	ACCCUCCAGUAAGUGUUA	2156
9093	UUCUGUUAAGAGUAACA	506	9093	UUCUGUUAAGAGUAACA	506	9111	UGUUAUACUUAACAGAA	2157
9111	AACUUAUUGAGUGAGUAC	507	9111	AACUUAUUGAGUGAGUAC	507	9129	GUACUGAGCAUAAAAGU	2158
9129	CUGUAGACUAGGUAUAGC	508	9129	CUGUAGACUAGGUAUAGC	508	9147	GCAUGUACUAGUACAG	2159
9147	CGAAAGGUCAGAAGUAGGU	509	9147	CGAAAGGUCAGAAGUAGGU	509	9165	ACCUACUUGGACCUUUG	2160
9165	UAUUUGCCUACUACACAGU	510	9165	UAUUUGCCUACUACACAGU	510	9183	ACUGGUAGUAAGGCAAAUA	2161
9183	UGGUAGUAGGUAUUAU	511	9183	UGGUAGUAGGUAUUAU	511	9201	AUUAAGAACCCUACUACCA	2162
9201	UAUAGAGCAUUAACAGGCU	512	9201	UAUAGAGCAUUAACAGGCU	512	9219	AGCUUGUAUUGCUCAUUA	2163
9219	UCUAUCAGGAGUUAUCUGU	513	9219	UCUAUCAGGAGUUAUCUGU	513	9237	ACAGAAACUCCUGAUAGA	2164
9237	UGGUGUUAUGCGAUGAAU	514	9237	UGGUGUUAUGCGAUGAAU	514	9255	AUUAUGCAUUAACACCA	2165
9255	UCUAUAGCUAACUUAU	515	9255	UCUAUAGCUAACUUAU	515	9273	AAAGAUGUUAUUAUGAGA	2166
9273	UACUCCUUAUGCAACCU	516	9273	UACUCCUUAUGCAACCU	516	9291	AGGUUGCACAAGAGGAGUA	2167
9291	UGUGGUGCUUAUAGUUGU	517	9291	UGUGGUGCUUAUAGUUGU	517	9309	CACAUUAAGCACCACCA	2168
9309	GUCUGUACUAGUAGGCU	518	9309	GUCUGUACUAGUAGGCU	518	9327	AGCCACUACUGAAGCAGAC	2169
9327	UGUGGUAUUAUUGCCAU	519	9327	UGUGGUAUUAUUGCCAU	519	9345	UAUGGCAUUAUACCACCA	2170
9345	AUUGGACUUAUGGUGCC	520	9345	AUUGGACUUAUGGUGCC	520	9363	GGCAGCACAAUACCCAAU	2171
9363	CUACUACUUAUUAUUAU	521	9363	CUACUACUUAUUAUUAU	521	9381	GAUUUCAAUUAAGUAG	2172
9381	CAGACGUAUUAUUGGUGAG	522	9381	CAGACGUAUUAUUGGUGAG	522	9399	CUCACAAUUAACGUGUG	2173
9399	GUACAACCAUUAUUGGCU	523	9399	GUACAACCAUUAUUGGCU	523	9417	AGCAACAAUUGGUUUAU	2174
9417	UGCUAAUUAUUAUUAUUA	524	9417	UGCUAAUUAUUAUUAUUA	524	9435	AAACAAUUAUUAUUAUUA	2175
9435	UUUGAUGCUUAUUAUUAU	525	9435	UUUGAUGCUUAUUAUUAU	525	9453	UAUAGGAAUUAUUAUUAU	2176
9453	ACUCUGUUAUUAUUAUUA	526	9453	ACUCUGUUAUUAUUAUUA	526	9471	AGCUUGUUAUUAUUAUUA	2177
9471	UAUACAGCUUAUUAUUAU	527	9471	UAUACAGCUUAUUAUUAU	527	9489	UCCCGGCAUUAUUAUUA	2178
9489	AGUCUACUUAUUAUUAU	528	9489	AGUCUACUUAUUAUUAU	528	9507	GUAAAAGUUAUUAUUAU	2179
9507	CUUGUACUUAUUAUUAU	529	9507	CUUGUACUUAUUAUUAU	529	9525	UAUAAUUAUUAUUAUUA	2180
9525	UUUACCAUUAUUAUUAU	530	9525	UUUACCAUUAUUAUUAU	530	9543	UGAAACUUAUUAUUAU	2181
9543	AUUCUUAUUAUUAUUAU	531	9543	AUUCUUAUUAUUAUUAU	531	9561	UUAAAGUUAUUAUUAU	2182
9561	AUGGUUAUUAUUAUUAU	532	9561	AUGGUUAUUAUUAUUAU	532	9579	AGAAAACUUAUUAUUAU	2183
9579	UCCUUAUUAUUAUUAU	533	9579	UCCUUAUUAUUAUUAU	533	9597	CCAAAAGGCAUUAUUAU	2184
9597	GAUAAAGCAUUAUUAU	534	9597	GAUAAAGCAUUAUUAU	534	9615	UACUUAUUAUUAUUAU	2185
9615	AUUCUGUUAUUAUUAU	535	9615	AUUCUGUUAUUAUUAU	535	9633	CUUCAGAAUUAUUAUUA	2186
9633	GCACUGCAUUAUUAUUA	536	9633	GCACUGCAUUAUUAUUA	536	9651	AAAGAACCAUUAUUAU	2187
9651	UAACAACUUAUUAUUAU	537	9651	UAACAACUUAUUAUUAU	537	9669	UUUCCUUAUUAUUAUUA	2188
9669	AAGAGUUAUUAUUAUUA	538	9669	AAGAGUUAUUAUUAUUA	538	9687	UCCAUUAUUAUUAUUA	2189
9687	AGUUAACUUAUUAUUAU	539	9687	AGUUAACUUAUUAUUAU	539	9705	GAAGUUAUUAUUAUUA	2190
9705	CGAGGAGGCUUAUUAU	540	9705	CGAGGAGGCUUAUUAU	540	9723	ACACAAAGCAGCCUUAU	2191

(400/110\_US)

9723	UACCUUUUUUGCUACAAG	541	9723	UACCUUUUUUGCUACAAG	541	9741	CUUUUGAGCAAAAAGGUA	2182
9741	GGAUUUUUACCUAAAUG	542	9741	GGAUUUUUACCUAAAUG	542	9759	CAUUUUAGGUACUUUCC	2183
9759	GCGUAGGAGACACUGUG	543	9759	GCGUAGGAGACACUGUG	543	9777	CAACAGUGUCUGGCUAGCG	2184
9777	GCCACUUACACAGUAAC	544	9777	GCCACUUACACAGUAAC	544	9795	GUUAUACUGUGUAAGGCG	2185
9795	CAGGUUUCUUGCUCUAU	545	9795	CAGGUUUCUUGCUCUAU	545	9813	AUAUAGAGCAAGUAAGGUG	2186
9813	UAACAAGUACAAGUAUUC	546	9813	UAACAAGUACAAGUAUUC	546	9831	GAUAUACUGUACUUUGUA	2187
9831	CAGUGGAGCCUUAAGUACU	547	9831	CAGUGGAGCCUUAAGUACU	547	9849	AGUAUUAAGGCUCCACUG	2188
9849	UACACGUAUCUGUGAAGCA	548	9849	UACACGUAUCUGUGAAGCA	548	9867	UGCUUACGUAUGGUGUA	2189
9867	AGCUUGGUGCCACUUAAGCA	549	9867	AGCUUGGUGCCACUUAAGCA	549	9885	UUGUAAGUGGCAAGCAAGCU	2190
9885	AAAGGCUUAUUAAGUACU	550	9885	AAAGGCUUAUUAAGUACU	550	9903	AAAGUACUUUAGAGGCUUU	2201
9903	UAGCAACUCAGGUGCUGAU	551	9903	UAGCAACUCAGGUGCUGAU	551	9921	AUAGCAACCUAGAGUUGCUA	2202
9921	UGUUCUUAACCAACACCA	552	9921	UGUUCUUAACCAACACCA	552	9939	UGGUGGUUGUAGAGAGACA	2203
9939	ACAGACAUCAUACAUUCU	553	9939	ACAGACAUCAUACAUUCU	553	9957	AGAAGUAUUGUUGUCUGU	2204
9957	UGCUGUUCGACAGUGGU	554	9957	UGCUGUUCGACAGUGGU	554	9975	ACCACUCUGCAGACACAGA	2205
9975	UUUAGGAAAUGGCAUUC	555	9975	UUUAGGAAAUGGCAUUC	555	9993	GAUUGCAUUUUCUAAAA	2206
9993	CCGUGAGGCAAGUUGAA	556	9993	CCGUGAGGCAAGUUGAA	556	10011	UUCACUUUUGCCUGACGGG	2207
10011	AGGGUGCAUGGUACAAGUA	557	10011	AGGGUGCAUGGUACAAGUA	557	10029	UACUUGUACCAUGGCACCGU	2208
10029	AACCGUGGAACUACAACU	558	10029	AACCGUGGAACUACAACU	558	10047	AGUUGUAGUUCACAGGUU	2209
10047	UCUUAUUGGAUUGUGUGU	559	10047	UCUUAUUGGAUUGUGUGU	559	10065	ACACCACAUUCCAUUAGA	2210
10065	GGAUGACACAGUAUACUGU	560	10065	GGAUGACACAGUAUACUGU	560	10083	ACAGUAUACUGUGUACUCC	2211
10083	UCCAAGACAUUGCUAUUGC	561	10083	UCCAAGACAUUGCUAUUGC	561	10101	GCAAUUGACAUUGCUUJGA	2212
10101	CACAGCAGAAAGACUGCU	562	10101	CACAGCAGAAAGACUGCU	562	10119	AAGCAUGUCUUCUGCUGU	2213
10119	UAUCCUAACUAUGAAGAU	563	10119	UAUCCUAACUAUGAAGAU	563	10137	AUCUUAUUGUAGGUAUUA	2214
10137	UCUGCUCAUUCGCAAUCC	564	10137	UCUGCUCAUUCGCAAUCC	564	10155	GGAUUUGGAAUAGAGAGA	2215
10155	CAACCAUAGCUUUCUUGUU	565	10155	CAACCAUAGCUUUCUUGUU	565	10173	AACAAGAAAGCUAUGGUUG	2216
10173	UCAGGCGGCAAGUUAUCAA	566	10173	UCAGGCGGCAAGUUAUCAA	566	10191	UUGAACAUUUGCCAGCCUGA	2217
10191	ACUUCGUGUUAUUGGCCAU	567	10191	ACUUCGUGUUAUUGGCCAU	567	10209	AUGGCCAAUAAACACGAGU	2218
10209	UUCUAUGCAAAUUGUCUG	568	10209	UUCUAUGCAAAUUGUCUG	568	10227	CAGACAAUUIUGCAUAGAA	2219
10227	GCUUAGGCUUAAAGUUGAU	569	10227	GCUUAGGCUUAAAGUUGAU	569	10245	AUCAACUUUAAAGCCUAGC	2220
10245	UACUUCUAACCCUAAGACA	570	10245	UACUUCUAACCCUAAGACA	570	10263	UGUCUUAAGGCUUUAAGUA	2221
10263	ACCAAGUAUAAAUUUGUC	571	10263	ACCAAGUAUAAAUUUGUC	571	10281	GACAAUUUUAUACUUGGU	2222
10281	CCGUUACCAACCCUGGUCAA	572	10281	CCGUUACCAACCCUGGUCAA	572	10299	UUGACAGGUUGGAUACGG	2223
10299	AACAUUUUCAGUUCUAGCA	573	10299	AACAUUUUCAGUUCUAGCA	573	10317	UGCUAAGAGUGAAAAUUGU	2224
10317	AUGCUACAAGUUGUACCA	574	10317	AUGCUACAAGUUGUACCA	574	10335	UGGUGAAACCAUUGUAGCAU	2225
10335	AUCUGGUGUUAUACAGUGU	575	10335	AUCUGGUGUUAUACAGUGU	575	10353	ACACUGAAUAAACACACAGU	2226
10353	UGCCAUGAGACCCUAAUACU	576	10353	UGCCAUGAGACCCUAAUACU	576	10371	AUGAUUAGGUCUCUAGGCA	2227
10371	UACCAUUAAGGUUCUUCU	577	10371	UACCAUUAAGGUUCUUCU	577	10389	GAAGAACCUIUUAUUGGUA	2228
10389	CCUUAUAGGAUUGGUGGU	578	10389	CCUUAUAGGAUUGGUGGU	578	10407	ACCAAGUAGCCAUUAGG	2229
10407	UAGUGUUGGUUUUAACAUU	579	10407	UAGUGUUGGUUUUAACAUU	579	10425	AUUGUUAUAAACCAACACUA	2230
10425	UGAUUAUGAUUGCGUGUCU	580	10425	UGAUUAUGAUUGCGUGUCU	580	10443	AGACACGCAUUAUUAUUA	2231
10443	UUUCUGCUUAUUGCAUCAU	581	10443	UUUCUGCUUAUUGCAUCAU	581	10461	AUGAGCAUUAUAGCAGAAA	2232
10461	UAUGGAGCUUCCAACAGGA	582	10461	UAUGGAGCUUCCAACAGGA	582	10479	UCCUGUUGGAAGGUCCAU	2233

(400/110\_US)

10479	AGUACACGCGUACUGAC	583	10479	AGUACACGCGUACUGAC	583	10497	GUACAGUACGCGUACU	2234
10497	CUUAGAAAGGUAUUUUAU	584	10497	CUUAGAAAGGUAUUUUAU	584	10515	AUAGAAUUUUAUUUAU	2235
10515	UGGUCUAUUUGUACAGA	585	10515	UGGUCUAUUUGUACAGA	585	10533	UCUGUACAAAUUGGACCA	2236
10533	ACAAACUGCAGCGUGCA	586	10533	ACAAACUGCAGCGUGCA	586	10551	UGCAGCCUGUGCAGUUUGU	2237
10551	AGGUACGACACACCAUA	587	10551	AGGUACGACACACCAUA	587	10569	UAUGGUUGUGUGUACCU	2238
10569	AACAUAAAUUUUUGGCA	588	10569	AACAUAAAUUUUUGGCA	588	10587	UGCAAAACAUUUUAUUGU	2239
10587	AUGGUGUAGUGUGU	589	10587	AUGGUGUAGUGUGU	589	10605	ACACGAGCAUACGCAU	2240
10605	UAUCAAUGGUAUAGGUG	590	10605	UAUCAAUGGUAUAGGUG	590	10623	CAACCUACACCAUUAU	2241
10623	GUUUCUAUAUAGAUUAC	591	10623	GUUUCUAUAUAGAUUAC	591	10641	GGUGAAUCUAUAAAGAAC	2242
10641	CACUACUUUGAAUGACUU	592	10641	CACUACUUUGAAUGACUU	592	10659	AAAGUCAUUAUAAAGUAG	2243
10659	UAACCUUGGCAUAGG	593	10659	UAACCUUGGCAUAGG	593	10677	CUUACUUGCCACAAAGUUA	2244
10677	GUACAAUAUAGACUUUG	594	10677	GUACAAUAUAGACUUUG	594	10695	CAAGGUUUAUAGUUGAC	2245
10695	GACAAAGAUUAUUGAC	595	10695	GACAAAGAUUAUUGAC	595	10713	GUCAACUAUUAUUGUGUC	2246
10713	CAUUAUUGGACCUUUCU	596	10713	CAUUAUUGGACCUUUCU	596	10731	AGAAAGGUGCCCAUUAUG	2247
10731	UGCUCAAACGAAUUGCC	597	10731	UGCUCAAACGAAUUGCC	597	10749	GGCAAUUCCUGUUUGGCA	2248
10749	CGUCUUAUUAUUGUGCU	598	10749	CGUCUUAUUAUUGUGCU	598	10767	AGCACACUAUUAUAGACG	2249
10767	UGCUUUGAAAGGUGUG	599	10767	UGCUUUGAAAGGUGUG	599	10785	CAGCAGCUUUAUAAAGCA	2250
10785	GCAGAAUGGUAUAGUUG	600	10785	GCAGAAUGGUAUAGUUG	600	10803	ACCAUUAUUAUUAUUGC	2251
10803	UCGUACUUAUUGUAGC	601	10803	UCGUACUUAUUGUAGC	601	10821	GUCAUUAUUAUUAUAGU	2252
10821	CACUUAUUAUUAUAGAG	602	10821	CACUUAUUAUUAUAGAG	602	10839	CUCAUUAUUAUUAUAGU	2253
10839	GUUUAACCAUUAUUAUAG	603	10839	GUUUAACCAUUAUUAUAG	603	10857	AACAUAUUAUUAUUAUAG	2254
10857	UGUUAACCAUUAUUAUAG	604	10857	UGUUAACCAUUAUUAUAG	604	10875	ACCAGCAUUAUUAUUAAG	2255
10875	GUUUAACCAUUAUUAUAG	605	10875	GUUUAACCAUUAUUAUAG	605	10893	CUUACCUUGGAAUUAUAG	2256
10893	GUUUAACCAUUAUUAUAG	606	10893	GUUUAACCAUUAUUAUAG	606	10911	CUUUAACCUUUAUUAUAG	2257
10911	GGGCACUUAUUAUUAUAG	607	10911	GGGCACUUAUUAUUAUAG	607	10929	CUUUAACCUUUAUUAUAG	2258
10929	GGGCACUUAUUAUUAUAG	608	10929	GGGCACUUAUUAUUAUAG	608	10947	UGUUAACCUUUAUUAUAG	2259
10947	UCAAAGUUAUUAUUAUAG	609	10947	UCAAAGUUAUUAUUAUAG	609	10965	AACAAGUUAUUAUUAUAG	2260
10965	UCAAAGUUAUUAUUAUAG	610	10965	UCAAAGUUAUUAUUAUAG	610	10983	UGACCAUUAUUAUUAUAG	2261
10983	ACUGUUUUUUUUUUUAU	611	10983	ACUGUUUUUUUUUUUAU	611	11001	GUAAACAAAGAAUUAUAG	2262
11001	CGAGAAUGCUUUAUUAUAG	612	11001	CGAGAAUGCUUUAUUAUAG	612	11019	UGGCAAGAAUUAUUAUAG	2263
11019	AUUUAUUAUUAUUAUAG	613	11019	AUUUAUUAUUAUUAUAG	613	11037	CAUUAUUAUUAUUAUAG	2264
11037	GGCAUUAUUAUUAUUAUAG	614	11037	GGCAUUAUUAUUAUUAUAG	614	11055	AGCAUUAUUAUUAUUAUAG	2265
11055	UAUGCUUUAUUAUUAUAG	615	11055	UAUGCUUUAUUAUUAUAG	615	11073	AGCUUUAUUAUUAUUAUAG	2266
11073	UAAGCAUUAUUAUUAUAG	616	11073	UAAGCAUUAUUAUUAUAG	616	11091	GCACAAGUUAUUAUUAUAG	2267
11091	CUUUAUUAUUAUUAUUAUAG	617	11091	CUUUAUUAUUAUUAUUAUAG	617	11109	AGAAGUUAUUAUUAUUAUAG	2268
11109	UCUUAUUAUUAUUAUUAUAG	618	11109	UCUUAUUAUUAUUAUUAUAG	618	11127	GUAGCAUUAUUAUUAUUAUAG	2269
11127	CUUUAUUAUUAUUAUUAUAG	619	11127	CUUUAUUAUUAUUAUUAUAG	619	11145	CAUGUUAUUAUUAUUAUUAUAG	2270
11145	GCUGUUAUUAUUAUUAUUAUAG	620	11145	GCUGUUAUUAUUAUUAUUAUAG	620	11163	CAUUAUUAUUAUUAUUAUUAUAG	2271
11163	GCUGUUAUUAUUAUUAUUAUAG	621	11163	GCUGUUAUUAUUAUUAUUAUAG	621	11181	AGCUUUAUUAUUAUUAUUAUUAUAG	2272
11181	UGAUUAUUAUUAUUAUUAUUAUAG	622	11181	UGAUUAUUAUUAUUAUUAUUAUAG	622	11199	GUAGUUAUUAUUAUUAUUAUUAUAG	2273
11199	CUUGCUUUAUUAUUAUUAUUAUAG	623	11199	CUUGCUUUAUUAUUAUUAUUAUAG	623	11217	AGCCUUAUUAUUAUUAUUAUUAUAG	2274
11217	UAAGGAUUAUUAUUAUUAUUAUAG	624	11217	UAAGGAUUAUUAUUAUUAUUAUAG	624	11235	AUACAUAUUAUUAUUAUUAUUAUAG	2275



(400/110\_US)

11235	UGCUUCAGCUUUAGUUUUG	625	11235	UGCUUCAGCUUUAGUUUUG	625	11253	CAAAACUAAAGCUGAAGCA	2276
11253	GCUUUAUCUAGACAGCU	626	11253	GCUUUAUCUAGACAGCU	626	11271	AGCUGUCUUAAGCUGAAGC	2277
11271	UGCAGCUGUUUAUGAU	627	11271	UGCAGCUGUUUAUGAU	627	11289	AUCAUCAAAACAGUGCGA	2278
11289	UGCUGUAGACGUGUUGG	628	11289	UGCUGUAGACGUGUUGG	628	11307	CCAAACACGUCUAGCAGCA	2279
11307	GACACUGAUGAAUGCAU	629	11307	GACACUGAUGAAUGCAU	629	11325	AUUGACAUUACUAGUGUC	2280
11325	UACACUUGUUUACAAAGUC	630	11325	UACACUUGUUUACAAAGUC	630	11343	GACUUUGUAAACAAAGUGUA	2281
11343	CUACUAGGUAAUGCUUA	631	11343	CUACUAGGUAAUGCUUA	631	11361	UAAAGCAUUAACCAUAGUAG	2282
11361	AGAUAAGCUAAUUGCAU	632	11361	AGAUAAGCUAAUUGCAU	632	11379	CAUGGAAUUAAGCUUAGUAG	2283
11379	GUGGGCUUUAAGCUUUCU	633	11379	GUGGGCUUUAAGCUUUCU	633	11397	AGAAUUAACUAAAGGCCAC	2284
11397	UGUAACCCUUAACUUAUCU	634	11397	UGUAACCCUUAACUUAUCU	634	11415	AGAAUUAAGAGGUUACA	2285
11415	UGGUGUCUUAACUUAUCU	635	11415	UGGUGUCUUAACUUAUCU	635	11433	AGAAUUAAGAGGUUACA	2286
11433	CAUGUUUUUAGCUAGAGCU	636	11433	CAUGUUUUUAGCUAGAGCU	636	11451	AGCUCUAGCUAAACCAUG	2287
11451	UGGUGUCUUAACUUAUCU	637	11451	UGGUGUCUUAACUUAUCU	637	11469	AACACACACAAACACUUA	2288
11469	UAGAGUUUUUGUGUGUU	638	11469	UAGAGUUUUUGUGUGUU	638	11487	UAAACUAGGUUAUACUCA	2289
11487	UAGAGUUUUUGUGUGUU	639	11487	UAGAGUUUUUGUGUGUU	639	11505	GGUGUUGCAGUAUAAAU	2290
11505	CUUACAGUUAACUAGCUU	640	11505	CUUACAGUUAACUAGCUU	640	11523	AAGCAUGAUAACUAGUAG	2291
11523	UGUUUUUUUUGUAGGC	641	11523	UGUUUUUUUUGUAGGC	641	11541	GCCUAGAAACAAUAAACA	2292
11541	CUUUGUUGCUGCUGUAC	642	11541	CUUUGUUGCUGCUGUAC	642	11559	GUAGCAGCAGCAACAAUAG	2293
11559	CUUUGGCCUUUUCUGUUUA	643	11559	CUUUGGCCUUUUCUGUUUA	643	11577	UAAACAGAAAGGCCAAAG	2294
11577	ACUACACCGUUAUCUAGG	644	11577	ACUACACCGUUAUCUAGG	644	11595	CCUAGAGUAAAGGUUAGU	2295
11595	GCUUACUUGGUGUUUAU	645	11595	GCUUACUUGGUGUUUAU	645	11613	UAAACACCAAGAGUAGC	2296
11613	UGACUACUUGGUGUUUAU	646	11613	UGACUACUUGGUGUUUAU	646	11631	UUAAGAGACCAAGUAGUA	2297
11631	ACAAGUUUUAGGUUAUAG	647	11631	ACAAGUUUUAGGUUAUAG	647	11649	CAUUAACCUAAUUCUUGU	2298
11649	GAACUCCAGGGCUUUG	648	11649	GAACUCCAGGGCUUUG	648	11667	CAAAAGCCUUGGGGUUC	2299
11667	GCCUCCUAAAGAGUUAU	649	11667	GCCUCCUAAAGAGUUAU	649	11685	AUAACUACUUAAGGAGGC	2300
11685	UGAUGCUUUAAGCUUAAC	650	11685	UGAUGCUUUAAGCUUAAC	650	11703	GUUAAGCUUUAAGGCAUCA	2301
11703	CAUUAAGUUUUGGUUAU	651	11703	CAUUAAGUUUUGGUUAU	651	11721	AUAACCAACAAUUAUAG	2302
11721	UGGAGGUAAACCAUUAUC	652	11721	UGGAGGUAAACCAUUAUC	652	11739	GAUACAUUGUUAACCUCCA	2303
11739	CAAGGUUGCUUUAAGUACAG	653	11739	CAAGGUUGCUUUAAGUACAG	653	11757	CUGUACAGUAGCAACCUUG	2304
11757	GUUUAAGUUUUGGUUAU	654	11757	GUUUAAGUUUUGGUUAU	654	11775	UACGUCAGCAUUAUUAAG	2305
11775	AAAGUGCACUUCUGGUA	655	11775	AAAGUGCACUUCUGGUA	655	11793	UACCAAGAUUGUGCACUUU	2306
11793	ACUGUCUUGGUUUAU	656	11793	ACUGUCUUGGUUUAU	656	11811	UUAAGAACCCGAGAGCAGU	2307
11811	ACAACUUAAGAGUAGUCA	657	11811	ACAACUUAAGAGUAGUCA	657	11829	UGACUCUACUUAAGUUGU	2308
11829	AUCUUAAGUUUGGGA	658	11829	AUCUUAAGUUUGGGA	658	11847	UGCCCAAAUUAAGUAGAU	2309
11847	ACAACUUAAGUUUGGGA	659	11847	ACAACUUAAGUUUGGGA	659	11865	GUGGAGUUGUACACAUUGU	2310
11865	CAUUAAGUUUUGGUUAU	660	11865	CAUUAAGUUUUGGUUAU	660	11883	UGCAAGAAUUAUUAUUG	2311
11883	AAAAGACAAACUUAAGCU	661	11883	AAAAGACAAACUUAAGCU	661	11901	AGCUUAGUUGUGUUGUUGU	2312
11901	UUUCGAGAAUGGUUUAU	662	11901	UUUCGAGAAUGGUUUAU	662	11919	AGAAACCAUUCUUCUGGAA	2313
11919	UUCUUGUUGUUGGUUUAU	663	11919	UUCUUGUUGUUGGUUUAU	663	11937	UAGCAAAACAGACAAAGA	2314
11937	AUCCAUUAGGUUGUUGU	664	11937	AUCCAUUAGGUUGUUGU	664	11955	UAGCAACCCUUGCAUGGUA	2315
11955	AGACAUUUAAGGUUGU	665	11955	AGACAUUUAAGGUUGU	665	11973	GCACAAACUUAUUAUUGUC	2316
11973	CGAGGAAUUGCUGUAUAC	666	11973	CGAGGAAUUGCUGUAUAC	666	11991	GUUAUCGAGCAUUAUCCUG	2317

(400/110\_US)

11991	CCGUGCUCACUCUUCAGGCU	667	11991	CCGUGCUCACUCUUCAGGCU	567	12009	AGCCUGAAGAGUAGCAGCGG	2318
12009	UAUUGCUUCAGAAUUUAGU	668	12009	UAUUGCUUCAGAAUUUAGU	668	12027	ACUAAUUUGUGAAGCAAAU	2319
12027	UUUUUUAACCAUAUAGCC	669	12027	UUUUUUAACCAUAUAGCC	669	12045	GGCAUUUGUGAAGAAAGAA	2320
12045	CGCUUAUGCCACUGCCAG	670	12045	CGCUUAUGCCACUGCCAG	670	12063	CUGGCAGUGGCAUAGCGG	2321
12063	GGAGGCCUAUAGCAGGCU	671	12063	GGAGGCCUAUAGCAGGCU	671	12081	AGCCUGCUCUAUAGGCCUCC	2322
12081	UGUAGCUAAUUGGUUAUUCU	672	12081	UGUAGCUAAUUGGUUAUUCU	672	12099	AGAUACCAUUAUAGCUACA	2323
12099	UGAAGUCGUUCUCAAAAAG	673	12099	UGAAGUCGUUCUCAAAAAG	673	12117	CUUUUUGAGAACGACUUCA	2324
12117	GUUAAAGAAUUCUUGAAU	674	12117	GUUAAAGAAUUCUUGAAU	674	12135	AUUCAAAGAUUUUUAUAAAC	2325
12135	UGUGGCUAAUUCUGAUUUU	675	12135	UGUGGCUAAUUCUGAUUUU	675	12153	AAACUCAGAUUUUAGCCACA	2326
12153	UGACCGUGAUGUGCCAGU	676	12153	UGACCGUGAUGUGCCAGU	676	12171	CAUGGCAGCAUCACGGUCA	2327
12171	GCAACGCAAGUUGGAAAAG	677	12171	GCAACGCAAGUUGGAAAAG	677	12189	CUUUUCCAAUUGCGUUGC	2328
12189	GAUGGCAGAUACGCUAUG	678	12189	GAUGGCAGAUACGCUAUG	678	12207	CAUAGCCUGAUCUGGCCAUC	2329
12207	GACCCAAUUGUACAAACAG	679	12207	GACCCAAUUGUACAAACAG	679	12225	CUGUUGUACAUUUUGGUC	2330
12225	GGCAAGAUUCAGGACAAG	680	12225	GGCAAGAUUCAGGACAAG	680	12243	CUUGUCCUCAGAUUUUGGCC	2331
12243	GAGGGCAAAAGUAACUAGU	681	12243	GAGGGCAAAAGUAACUAGU	681	12261	ACUAGUUAUUAUUGGCCGCA	2332
12261	UGCUAUGCAAAAUUGCUC	682	12261	UGCUAUGCAAAAUUGCUC	682	12279	GAGCAUUGUUUGCAUAGCA	2333
12279	CUUCACUAUGCUUAGGAAG	683	12279	CUUCACUAUGCUUAGGAAG	683	12297	CUUCCUAAAGCAUAGUAGG	2334
12297	GCUUGAAUUAUGACACUU	684	12297	GCUUGAAUUAUGACACUU	684	12315	AAGUCCAUUAUUAUCAAAGC	2335
12315	UAACAACAUUAUUAACAACAU	685	12315	UAACAACAUUAUUAACAACAU	685	12333	AUUGUUAUUAUUAUUGUUA	2336
12333	UGCGCGUAGUUGUUGUUU	686	12333	UGCGCGUAGUUGUUGUUU	686	12351	AACACAACCAUCACGGCGCA	2337
12351	UCCACUACAACAUUACCA	687	12351	UCCACUACAACAUUACCA	687	12369	UGUAUGUUGUUGAGUGGA	2338
12369	AUUGACUACAGCAGCCAAA	688	12369	AUUGACUACAGCAGCCAAA	688	12387	UUUGGUGUGUUGUAGUCAU	2339
12387	ACUCAUGGUUGUUGUCCCU	689	12387	ACUCAUGGUUGUUGUCCCU	689	12405	AGGACAACCAUUGAGU	2340
12405	UGAUUAUGGUUACCUACAAG	690	12405	UGAUUAUGGUUACCUACAAG	690	12423	CUUGUAGGUUACCAUUAUCA	2341
12423	GAACACUUGUAUGUAAC	691	12423	GAACACUUGUAUGUAAC	691	12441	GUUACCAUACCAUUGUUC	2342
12441	CACCUUAUUAUUGCAUCU	692	12441	CACCUUAUUAUUGCAUCU	692	12459	AGAUGCAUUAUUAUAGGUG	2343
12459	UGCACUCUGGGAUUAUCCAG	693	12459	UGCACUCUGGGAUUAUCCAG	693	12477	CUGGAUUAUUAUUAUAGUCA	2344
12477	GCAAGUUGUUGAUGCGGAU	694	12477	GCAAGUUGUUGAUGCGGAU	694	12495	AUCCGCAUACAACAUUUGC	2345
12495	UAGCAAGAUUUAUUAACUU	695	12495	UAGCAAGAUUUAUUAACUU	695	12513	AAGUUGAACAUCUUGCUA	2346
12513	UAGUGAAUUAUUAUAGGAC	696	12513	UAGUGAAUUAUUAUAGGAC	696	12531	GUCCAUUUUAUUAUUAUUAU	2347
12531	CAAUUACCAUUAUUAUUGCU	697	12531	CAAUUACCAUUAUUAUUGCU	697	12549	AGCCAAUUAUUGGUAUUG	2348
12549	UUGGCCUUAUUAUUAUUA	698	12549	UUGGCCUUAUUAUUAUUA	698	12567	UGUAACAUAUAGAGGCCAA	2349
12567	AGCUUAAGAGCCAAUUA	699	12567	AGCUUAAGAGCCAAUUA	699	12585	UGAUUGGCUUUAUAGGCU	2350
12585	AGCUUAUUAUUAUUAUUA	700	12585	AGCUUAUUAUUAUUAUUA	700	12603	AUUCUGUAUUAUUAUUAUUA	2351
12603	UAUUAACUAGUUAUUAUUA	701	12603	UAUUAACUAGUUAUUAUUA	701	12621	UACUGGACUUAUUAUUAUUA	2352
12621	AGCACUACGACAGAUUCC	702	12621	AGCACUACGACAGAUUCC	702	12639	GGACAUUGUUGUUAUUAUUA	2353
12639	CUUGCGGCUUGUUAUUAUUA	703	12639	CUUGCGGCUUGUUAUUAUUA	703	12657	UGUGGUACGACCGCACAG	2354
12657	ACAACAGCUUUAUUAUUAUUA	704	12657	ACAACAGCUUUAUUAUUAUUA	704	12675	AUCAGUACAAGCUUUAUUAUUA	2355
12675	UAGAAUUAUUAUUAUUAUUA	705	12675	UAGAAUUAUUAUUAUUAUUA	705	12693	GUAGGCAAGUUAUUAUUAUUA	2356
12693	CUAUAACAUAUUAUUAUUAUUA	706	12693	CUAUAACAUAUUAUUAUUAUUA	706	12711	UCCUUGGAAUUAUUAUUAUUA	2357
12711	AGGUAGGUUUAUUAUUAUUAUUA	707	12711	AGGUAGGUUUAUUAUUAUUAUUA	707	12729	UCCAGCAACAACCUUUAUUAUUA	2358
12729	AUUAUAUUAUUAUUAUUAUUA	708	12729	AUUAUAUUAUUAUUAUUAUUA	708	12747	UUGGUGGCUUAUUAUUAUUAUUA	2359

(400/110\_US)

12747	AGAUCUCAAUUGGCUAGA	709	12747	AGAUCUCAAUUGGCUAGA	709	12765	UCUAGCCCAUUUGAGAUUCU	2360
12765	AUUCUCAAAGAGUGUGU	710	12765	AUUCUCAAAGAGUGUGU	710	12783	ACCAUACACUCUJAGGGAU	2361
12783	UACAGGUACAUAUUACACA	711	12783	UACAGGUACAUAUUACACA	711	12801	UGAUAAAUGUACCUGUA	2362
12801	AGACUGGAACACCUJUGU	712	12801	AGACUGGAACACCUJUGU	712	12819	ACAAGGUGUCCACCUJUGU	2363
12819	UAGGUUUUGUAACAGACACA	713	12819	UAGGUUUUGUAACAGACACA	713	12837	UGUGUCUGUAACAACCCUA	2364
12837	ACCAAAAGGCGCUAAAGUG	714	12837	ACCAAAAGGCGCUAAAGUG	714	12855	CACUUAAGGCCUUUUGGU	2365
12855	GAUAUACUUGUACUUAUC	715	12855	GAUAUACUUGUACUUAUC	715	12873	GAUGAAGUACAAGUAUUUC	2366
12873	CAAAGGUUAACAACCUA	716	12873	CAAAGGUUAACAACCUA	716	12891	UAGGUUUUAAGCCUUUG	2367
12891	AAUAAGAGUUGGUGUG	717	12891	AAUAAGAGUUGGUGUG	717	12909	CAGCACAUAACCUUAUU	2368
12909	GGCAGUUUAGUGCUACA	718	12909	GGCAGUUUAGUGCUACA	718	12927	UGUAGCAGUAAACUGCCC	2369
12927	AGUACGUCUUCAGGCGUGA	719	12927	AGUACGUCUUCAGGCGUGA	719	12945	UCCAGCCUGAAGACGCUACU	2370
12945	AAUUGCUACAGAAGUACCU	720	12945	AAUUGCUACAGAAGUACCU	720	12963	AGGUACUUCUGUAGCAUUU	2371
12963	UGCCAAUUAACUGUGCUU	721	12963	UGCCAAUUAACUGUGCUU	721	12981	AAGCACAGUUGAUIUGGCA	2372
12981	UUCUUUCUGUGCUUUUGCA	722	12981	UUCUUUCUGUGCUUUUGCA	722	12999	UGCAAAAGCACAGAAAGGAA	2373
12999	AGUAGACCCUGCUAAAGCA	723	12999	AGUAGACCCUGCUAAAGCA	723	13017	UGCUUUAGCAGGGUCUACU	2374
13017	AUAUAAAGAUUACCUAGCA	724	13017	AUAUAAAGAUUACCUAGCA	724	13035	UGCJAGGUAAUCCUUUAU	2375
13035	AAGUGGAGGACAACCAUC	725	13035	AAGUGGAGGACAACCAUC	725	13053	GAUUGGUUGCCUCCAUU	2376
13053	CACCAACUGUGUGAAGAU	726	13053	CACCAACUGUGUGAAGAU	726	13071	CAUCUUCACACAGUUGGUG	2377
13071	GUUGUGUACACACACUGGU	727	13071	GUUGUGUACACACACUGGU	727	13089	ACCAGUGUGUACACAAC	2378
13089	UACAGGACAGGCAAUUACU	728	13089	UACAGGACAGGCAAUUACU	728	13107	AGUAUUUGCCUGUCCUGUA	2379
13107	UGUAACACAGAGCUAAC	729	13107	UGUAACACAGAGCUAAC	729	13125	GAUAGCUUCUGGUAUACA	2380
13125	CAGGACCAAGAGUCCUUU	730	13125	CAGGACCAAGAGUCCUUU	730	13143	AAAGGACUUGGUCCAUG	2381
13143	UGGUGGUGCUUCAUGUUGU	731	13143	UGGUGGUGCUUCAUGUUGU	731	13161	ACAACAUGAAGCACCACCA	2382
13161	UCUGUAUUUGAUAUCCAC	732	13161	UCUGUAUUUGAUAUCCAC	732	13179	GUGGCAUCUACAUAUACAGA	2383
13179	CAUUGACCAUCCAAUCCU	733	13179	CAUUGACCAUCCAAUCCU	733	13197	AGGAUUUGAUGGUCUAAUG	2384
13197	UAAAGGAUUCUGAGCUUG	734	13197	UAAAGGAUUCUGAGCUUG	734	13215	CAAGUACAGAAUCCUUAU	2385
13215	GAAGGUAAGUACGUCCAA	735	13215	GAAGGUAAGUACGUCCAA	735	13233	UUGGACGUACUUAACCUUUC	2386
13233	AAUACCUACCAUUGUGCU	736	13233	AAUACCUACCAUUGUGCU	736	13251	AGCACAAUGUGUAGGUUUU	2387
13251	UAUAGCCACAGUGGUUUU	737	13251	UAUAGCCACAGUGGUUUU	737	13269	AAACCCACUGGGUUAUUA	2388
13269	UACACUUAAGAAACACAGUC	738	13269	UACACUUAAGAAACACAGUC	738	13287	GACUGUGUUUCUUAAGUGUA	2389
13287	CUGUACCGUCUGCGGAUUG	739	13287	CUGUACCGUCUGCGGAUUG	739	13305	CAUUCGACAGCGGUACAG	2390
13305	GUGGAAAGGUUAUUGGUGU	740	13305	GUGGAAAGGUUAUUGGUGU	740	13323	ACAGCCAUAACCUUCCAC	2391
13323	UAGUUGAGCAACUCCGC	741	13323	UAGUUGAGCAACUCCGC	741	13341	GCGGAGUUGGUCACAAUA	2392
13341	CGAACCCUUGAUGCAGUCU	742	13341	CGAACCCUUGAUGCAGUCU	742	13359	AGACUGCAUCAAGGGUJUG	2393
13359	UGCGGAUGCAUCAACGUUU	743	13359	UGCGGAUGCAUCAACGUUU	743	13377	AAACGUUGAUGCAUCCGCA	2394
13377	UUUAAACGGGUUUUGCGUG	744	13377	UUUAAACGGGUUUUGCGUG	744	13395	CACCGCAAAACCCGUUUUAAA	2395
13395	GUAAGUGCAGCCCGUCUUA	745	13395	GUAAGUGCAGCCCGUCUUA	745	13413	UAAGAGCGGCGGCACUUAC	2396
13413	ACACCGUGGCGCACAGGCA	746	13413	ACACCGUGGCGCACAGGCA	746	13431	UGCCUGUGCCGACGCGUGU	2397
13431	ACUAGUACUGAUGUGUCU	747	13431	ACUAGUACUGAUGUGUCU	747	13449	AGACGACUACAGUACUAGU	2398
13449	UACAGGGCUUUUGAUUUU	748	13449	UACAGGGCUUUUGAUUUU	748	13467	AAUAUCAAAGGCCUGUA	2399
13467	UACAACGAAAAGUUGUGUG	749	13467	UACAACGAAAAGUUGUGUG	749	13485	CAGCAACUUUUUCGUUGUA	2400
13485	GGUUUUGCAAAAGUUCUUA	750	13485	GGUUUUGCAAAAGUUCUUA	750	13503	UUAGGAACUUUUGCAAAACC	2401



(400/110\_US)

13503	AAAACUAAUUGCUGCGU	751	13503	AAAACUAAUUGCUGCGU	751	13521	AGCGACGACAAUUAUUGUUU	2402
13521	UUCGAGGAGAGGAGG	752	13521	UUCGAGGAGAGGAGG	752	13539	CCUCAUCCUUCUGGAA	2403
13539	GAAGGCAUUAUUAUAGACU	753	13539	GAAGGCAUUAUUAUAGACU	753	13557	AGUCUAAUAAUUGCCUUC	2404
13557	UCUUAUUUGUAGUUAAGA	754	13557	UCUUAUUUGUAGUUAAGA	754	13575	UCUUAACUACAAAGUAAGA	2405
13575	AGGCAUACUAGUCUACU	755	13575	AGGCAUACUAGUCUACU	755	13593	AGUUAACUAAUUAUUGCCU	2406
13593	UACCAACUAGAGAGACUA	756	13593	UACCAACUAGAGAGACUA	756	13611	UAGUCUCUUAUUGUUA	2407
13611	AUUUAACUUGGUUAAAG	757	13611	AUUUAACUUGGUUAAAG	757	13629	CUUUAACCAAGUUAUAAU	2408
13629	GAUUGCCAGCGGUUGCUG	758	13629	GAUUGCCAGCGGUUGCUG	758	13647	CAGAACCCGUGGACAAUC	2409
13647	GUCAUGACUUUUCAAGU	759	13647	GUCAUGACUUUUCAAGU	759	13665	ACUUGAAAGUAGUAGGAC	2410
13665	UUUAGAGUAGUAGGAGACA	760	13665	UUUAGAGUAGUAGGAGACA	760	13683	UGUGACCAUCUACUCAA	2411
13683	AUGGUACCAUUAUAC	761	13683	AUGGUACCAUUAUAC	761	13701	GUGAUUAUUGUGGUACAU	2412
13701	CGUCAGCGUACUAAU	762	13701	CGUCAGCGUACUAAU	762	13719	AUUUAUUAUAGCGCUGAG	2413
13719	UACCAAUUGGCUAAUUAAG	763	13719	UACCAAUUGGCUAAUUAAG	763	13737	CUAAUUCAGCCAUUGUGUA	2414
13737	GUCAUUGCUCUACGUCAU	764	13737	GUCAUUGCUCUACGUCAU	764	13755	AAUGACGUAGAGCAUAGAC	2415
13755	UUUGAUGAGGUAUUGUG	765	13755	UUUGAUGAGGUAUUGUG	765	13773	CACAAUACCCUACUCAA	2416
13773	GAUACAUUAAAGAAUAC	766	13773	GAUACAUUAAAGAAUAC	766	13791	GUUUUCUUUUAUUGUAUC	2417
13791	CUCGUCACAUACAUAUUGCU	767	13791	CUCGUCACAUACAUAUUGCU	767	13809	AGCAUUUGUAUGUGACGAG	2418
13809	UGUGAUGAUGAUUAUUA	768	13809	UGUGAUGAUGAUUAUUA	768	13827	UGAAUUAUUAUUAUUA	2419
13827	AAUAAAGAGGUAUUGUAUG	769	13827	AAUAAAGAGGUAUUGUAUG	769	13845	CAUACCAUCCUUAUUAU	2420
13845	GACUUGGUAAGAAUCCUG	770	13845	GACUUGGUAAGAAUCCUG	770	13863	CAGGAUUCUACGGAAGUC	2421
13863	GACAUUUAUUGGUAUUG	771	13863	GACAUUUAUUGGUAUUG	771	13881	CAUACCGCUAAAGUAUUC	2422
13881	GUCAUUAUUGGAGCGUG	772	13881	GUCAUUAUUGGAGCGUG	772	13899	CAGCUCACCUAAAGUAUUC	2423
13899	GUACGCAUUAUUAUUA	773	13899	GUACGCAUUAUUAUUA	773	13917	UUAUUAUUAUUGGCGUAC	2424
13917	AAGACUGUAUUAUUCGCG	774	13917	AAGACUGUAUUAUUCGCG	774	13935	CGCAGAAUUGUACAGUCUU	2425
13935	GAUGCUAUGCGUAGCAG	775	13935	GAUGCUAUGCGUAGCAG	775	13953	CUAGCUCACGCUAGCAUC	2426
13953	GGCAUUGUAGGCGUACUGA	776	13953	GGCAUUGUAGGCGUACUGA	776	13971	UCAGUACGCCUACAAUGCC	2427
13971	ACAUUAGAUUAUCAGGAUC	777	13971	ACAUUAGAUUAUCAGGAUC	777	13989	GAUCUGAUUAUCUAAUGU	2428
13989	CUUAAUUGGAAUUAUUCG	778	13989	CUUAAUUGGAAUUAUUCG	778	14007	CGUACCAUUCUCCAUUAAG	2429
14007	GAUUUGGUAUUAUUCGUAC	779	14007	GAUUUGGUAUUAUUCGUAC	779	14025	GUACGAAUUCACCCGAAUUC	2430
14025	CAAGUAGCACCAGGCGUG	780	14025	CAAGUAGCACCAGGCGUG	780	14043	CGCAGCCUGGUGCUACUUG	2431
14043	GGAGUUCUUAUUGGUAU	781	14043	GGAGUUCUUAUUGGUAU	781	14061	AUCCACAAUAGGGAUCC	2432
14061	UCAUUAUUAUUAUUGCUGA	782	14061	UCAUUAUUAUUAUUGCUGA	782	14079	UCAGCAUUGAGUAAUUAUGA	2433
14079	AUGCCCAUCCUACUUA	783	14079	AUGCCCAUCCUACUUA	783	14097	UCAAGUGAGGAGGGAU	2434
14097	ACUAGGCAUUGGCGUG	784	14097	ACUAGGCAUUGGCGUG	784	14115	CAGCAGCAUUGCCUAGU	2435
14115	GAGUCCCAUUAUUGGUAU	785	14115	GAGUCCCAUUAUUGGUAU	785	14133	CAGCAUCCAUUAGGGAUCC	2436
14133	GAUCUGGCAUUAUUGCUGA	786	14133	GAUCUGGCAUUAUUGCUGA	786	14151	UAAGUGGUUUUGCGAUUC	2437
14151	AUAUAGGUAUUAUUGCUGA	787	14151	AUAUAGGUAUUAUUGCUGA	787	14169	UCAGCAUUAUUAUUAUUAU	2438
14169	AAUUAUUAUUAUUAUUAU	788	14169	AAUUAUUAUUAUUAUUAU	788	14187	CUUCCGUAAUUAUUAUUAU	2439
14187	GAGAGACUUAUUAUUAUUAU	789	14187	GAGAGACUUAUUAUUAUUAU	789	14205	CGAAGACAAAGUCUCUC	2440
14205	GACCGUUAUUAUUAUUAU	790	14205	GACCGUUAUUAUUAUUAU	790	14223	AAUUAUUAUUAUUAUUAU	2441
14223	UGGACCAUUAUUAUUAUUAU	791	14223	UGGACCAUUAUUAUUAUUAU	791	14241	GAUGGUUAUUGUGGUGGUAU	2442
14241	CCCAUUAUUAUUAUUAUUAU	792	14241	CCCAUUAUUAUUAUUAUUAU	792	14259	AACGUAUUAUUAUUAUUAU	2443

(400/110\_US)

14259	UUGGAUGAUAGGUGUAUCC	793	14259	UUGGAUGAUAGGUGUAUCC	793	14277	GGAUACACCUUAUCAUCAA	2444
14277	CUUCUUGUGCAACCUUUA	794	14277	CUUCUUGUGCAACCUUUA	794	14295	UAAAGUUGCACAAUGAAG	2445
14295	AUGUGUUAUUUCUACUG	795	14295	AUGUGUUAUUUCUACUG	795	14313	CAGUAGAAAUUAACACAUU	2446
14313	GUGUUCACCUACAAGUU	796	14313	GUGUUCACCUACAAGUU	796	14331	CAGUAGUAGGUGGAAACAC	2447
14331	UUGGACCACUAGUAGAA	797	14331	UUGGACCACUAGUAGAA	797	14349	UUCUUAUUAUUGGUCACAA	2448
14349	AAAUUAUUUGAUGGUG	798	14349	AAAUUAUUUGAUGGUG	798	14367	CACCAUCUACAAAUUUUU	2449
14367	GUCCUUUUUGUUUCAA	799	14367	GUCCUUUUUGUUUCAA	799	14385	UUGAAACACAAAGGAAC	2450
14385	ACUGGAUACCUUUUCUG	800	14385	ACUGGAUACCUUUUCUG	800	14403	CACGAAUUGGUUCCAGU	2451
14403	GAGUAGGAGUGCUACAUA	801	14403	GAGUAGGAGUGCUACAUA	801	14421	UAUGUACGACUCCUACUC	2452
14421	AUACAGGAUGUAACUUA	802	14421	AUACAGGAUGUAACUUA	802	14439	GUAGUUUAUUAUCCUGAUU	2453
14439	CAUAGCUCGCGUCACAGU	803	14439	CAUAGCUCGCGUCACAGU	803	14457	AACUGAGACGCGAGCUAUG	2454
14457	UUCAGGAAUUAUUGUGU	804	14457	UUCAGGAAUUAUUGUGU	804	14475	ACACUAAAAGUUCUUAUAA	2455
14475	UAUGCUGCUGAUCAGCUA	805	14475	UAUGCUGCUGAUCAGCUA	805	14493	UAGCUGGAUCAGGACUAU	2456
14493	AUGCAUGCAGCUUGGCA	806	14493	AUGCAUGCAGCUUGGCA	806	14511	UGCCAGAAAGUGCAUGCAU	2457
14511	AAUUAUUGCUAGUAUAA	807	14511	AAUUAUUGCUAGUAUAA	807	14529	GUUUAUCUAGCAUUAUUU	2458
14529	CGCACUACUUGCUUUUCAG	808	14529	CGCACUACUUGCUUUUCAG	808	14547	CUGAAAGCAUGUAGUGCG	2459
14547	GUAGCUGCACAACAAACA	809	14547	GUAGCUGCACAACAAACA	809	14565	UGUUUUUAGUGGACUAC	2460
14565	AAUGUUGCUUUUCAAACUG	810	14565	AAUGUUGCUUUUCAAACUG	810	14583	CAGUUAUAAAGCAACAUU	2461
14583	GUCAAAACCGGUAAUUUA	811	14583	GUCAAAACCGGUAAUUUA	811	14601	UAAAUAUACCGGUUUUGAC	2462
14601	AAUAAAGACUUUAUGACU	812	14601	AAUAAAGACUUUAUGACU	812	14619	AGUCAUAAAGUCUUAUUA	2463
14619	UUUGCUGUGCUAAAGGUU	813	14619	UUUGCUGUGCUAAAGGUU	813	14637	AACUUUAAGCACACAGCAA	2464
14637	UUCUUUAAGGAAGGAUUG	814	14637	UUCUUUAAGGAAGGAUUG	814	14655	AACUUCUUCUUAAGAA	2465
14655	UCUGUUGAACUAAACACU	815	14655	UCUGUUGAACUAAACACU	815	14673	AGUGUUUAUAGUUUCAAACA	2466
14673	UUCUUCUUGCUCAGGAUG	816	14673	UUCUUCUUGCUCAGGAUG	816	14691	CAUCCUGAGCAAAAGAA	2467
14691	GGCAACGCGCUAUACUGUG	817	14691	GGCAACGCGCUAUACUGUG	817	14709	CACUGAUAGCAGCGUUGCC	2468
14709	GAUUAUGACUUAUUCGUU	818	14709	GAUUAUGACUUAUUCGUU	818	14727	AACGAUUAUAGCUAAUUA	2469
14727	UAUAAUCUGCCCAACAUUG	819	14727	UAUAAUCUGCCCAACAUUG	819	14745	ACAUUGUUGCAGAUUAUA	2470
14745	UGUGAUUAUCAGAACUCC	820	14745	UGUGAUUAUCAGAACUCC	820	14763	GGAGUUGUCUGAUUAUCACA	2471
14763	CUAUUCGUAUUGAAGUUG	821	14763	CUAUUCGUAUUGAAGUUG	821	14781	CAACUUAACUACGAAUAG	2472
14781	GUUGAAUUAUUAUUGAUU	822	14781	GUUGAAUUAUUAUUGAUU	822	14799	AAUCAAAGUUAUUAUCAA	2473
14799	UGUUAACGAUGGUGGUGUA	823	14799	UGUUAACGAUGGUGGUGUA	823	14817	UACAGCCACCAUCGUAACA	2474
14817	AUUAUUGCCAAACGAUAA	824	14817	AUUAUUGCCAAACGAUAA	824	14835	UAACUUGGUUGGCAUUAU	2475
14835	AUCGUUAACAUCUGGAUA	825	14835	AUCGUUAACAUCUGGAUA	825	14853	UAUCCAGAUUGUUAACGAU	2476
14853	AAUACAGCUGGUUCCCAU	826	14853	AAUACAGCUGGUUCCCAU	826	14871	AUGGAAACCCAGCUGAUUU	2477
14871	UUUAUAAAUUGGGUAAAG	827	14871	UUUAUAAAUUGGGUAAAG	827	14889	CCUUAACCCCAUUUUUAAA	2478
14889	GCUAGACUUUAUUAUGACU	828	14889	GCUAGACUUUAUUAUGACU	828	14907	AGUCAUUAUAAAGUUAAG	2479
14907	UCAAUGAUUAUGAGGAUC	829	14907	UCAAUGAUUAUGAGGAUC	829	14925	GAUCCUGAUAAACUUAUA	2480
14925	CAAGAUGCACUUUUCGCGU	830	14925	CAAGAUGCACUUUUCGCGU	830	14943	ACGCGAAAGUGCAUCUUG	2481
14943	UAUACUAAAGGUUAUUGCA	831	14943	UAUACUAAAGGUUAUUGCA	831	14961	UGACAUUAACGCUUAGUAUA	2482
14961	AUCCUUAACUUAUUAUUA	832	14961	AUCCUUAACUUAUUAUUA	832	14979	UUGAGUUAUUAUUAUUA	2483
14979	AUGAAUCUUAAGUAUGCCA	833	14979	AUGAAUCUUAAGUAUGCCA	833	14997	UUGCAUUAUUAAGUAUUA	2484
14997	AUUAUGCAAAAGAAUAGAG	834	14997	AUUAUGCAAAAGAAUAGAG	834	15015	CUCUAUUAUUAUUAUUA	2485

(400/110\_US)

15015	GCUCGACCGUAGCUGGUG	835	15015	GCUCGACCGUAGCUGGUG	835	15033	CACCAGCUACGGUGCGAGC	2486
15033	GUCUCUACUCUGUAGUACUA	836	15033	GUCUCUACUCUGUAGUACUA	836	15051	UAGUACUACAGAUAGAGAC	2487
15051	AUGACAAUAGACAGUUC	837	15051	AUGACAAUAGACAGUUC	837	15069	GAACUGUCUUAUUGUACU	2488
15069	CAUCAGAAUUAUUGAAGU	838	15069	CAUCAGAAUUAUUGAAGU	838	15087	ACUUCAAUUAUUCUGAUG	2489
15087	UCAUAGCCGACUAGAG	839	15087	UCAUAGCCGACUAGAG	839	15105	CACUAGUGGCGGCUAUGA	2490
15105	GGAGCUACUGUGUAUUG	840	15105	GGAGCUACUGUGUAUUG	840	15123	CAUUAACACAGUAGCUCC	2491
15123	GGAAAGCAAGUUAUUG	841	15123	GGAAAGCAAGUUAUUG	841	15141	CGUAAACUUGCUUUGCC	2492
15141	GGUGGCGGCAUUAUUG	842	15141	GGUGGCGGCAUUAUUG	842	15159	ACAUUAUUGCCAGCCACC	2493
15159	UUAUAAACUGUUAACAGUG	843	15159	UUAUAAACUGUUAACAGUG	843	15177	CACUGAAACAGUUUUUAA	2494
15177	GAUGUAGAAUCCACACC	844	15177	GAUGUAGAAUCCACACC	844	15195	GGUGGAGUUAUUCACUAC	2495
15195	CUUAUGGUGUUGGUAUUC	845	15195	CUUAUGGUGUUGGUAUUC	845	15213	GAUUAUCCAAACCAUAG	2496
15213	CCAAUUGGUGGUAUUC	846	15213	CCAAUUGGUGGUAUUC	846	15231	UGGCUUGUACAUUUGG	2497
15231	AUGCCUAAACUGCUAAGGA	847	15231	AUGCCUAAACUGCUAAGGA	847	15249	UCCUAGCAUGUUAAGCAU	2498
15249	AUAUUGGCGUUCUUGUUC	848	15249	AUAUUGGCGUUCUUGUUC	848	15267	GAACAAGAGGCGCAUUAU	2499
15267	CUUGCUCGCAACAUACA	849	15267	CUUGCUCGCAACAUACA	849	15285	UGUUAUGUUGCGAGCAAG	2500
15285	ACUUGCUUAACUUAUCAC	850	15285	ACUUGCUUAACUUAUCAC	850	15303	GUGAUAAGUUAACGAAU	2501
15303	CACCGUUCUACAGGUUAG	851	15303	CACCGUUCUACAGGUUAG	851	15321	CUAACUGUAGAAACGGUG	2502
15321	GCUAACGAGUGGCGCAAG	852	15321	GCUAACGAGUGGCGCAAG	852	15339	CUUGCGCACUCUGUAGC	2503
15339	GUUAUAGUGAGUUGUUA	853	15339	GUUAUAGUGAGUUGUUA	853	15357	UAGCCAUUCACUUAUAC	2504
15357	AUGUGUGGCGGCUACUUA	854	15357	AUGUGUGGCGGCUACUUA	854	15375	AUAGGAGCGCCACACAU	2505
15375	UAUUAUAAACAGGUGGAA	855	15375	UAUUAUAAACAGGUGGAA	855	15393	UCCACUGUUAUUAACUA	2506
15393	ACAUCUCCGGUGUAGUUA	856	15393	ACAUCUCCGGUGUAGUUA	856	15411	UAGCAUCACCGGAGUAGU	2507
15411	ACAACUGCUUAUGCUAUA	857	15411	ACAACUGCUUAUGCUAUA	857	15429	UAUUAAGUUAAGAGACU	2508
15429	AGUGUCUUAACAUUUGUC	858	15429	AGUGUCUUAACAUUUGUC	858	15447	GACAALUGUUAAGAGACU	2509
15447	CAAGCUGUUAACAGCCAAUG	859	15447	CAAGCUGUUAACAGCCAAUG	859	15465	CAUUGGCGUUAACAGCUUG	2510
15465	GUAAUUGCAUUCUUAAC	860	15465	GUAAUUGCAUUCUUAAC	860	15483	UUGAAAGAGUGCAUUAAC	2511
15483	ACUGAUGGUUAUAGUAG	861	15483	ACUGAUGGUUAUAGUAG	861	15501	CUAUCUUAUUAUCCAUCAU	2512
15501	GCUGACAAGUAGUCCGCA	862	15501	GCUGACAAGUAGUCCGCA	862	15519	UGCGGACAUUUGUCAGC	2513
15519	AUUCUACAAACAGGCUUC	863	15519	AUUCUACAAACAGGCUUC	863	15537	AGAGCCUGUGUUGUAGAUU	2514
15537	UAUGAGUGUCUUAUAGAA	864	15537	UAUGAGUGUCUUAUAGAA	864	15555	UUCUAUAGACACUUAU	2515
15555	AAUAGGGAUGUUAUAG	865	15555	AAUAGGGAUGUUAUAG	865	15573	CAUGAUCACAUCCCUAUA	2516
15573	GAAUUGGUGGAGUUAUUA	866	15573	GAAUUGGUGGAGUUAUUA	866	15591	AAACUACUCCACGAAUUC	2517
15591	UACGCUUACCGGUAUUAAC	867	15591	UACGCUUACCGGUAUUAAC	867	15609	GUUACGCGAGUUAAGCGUA	2518
15609	CAUUCUCCAUAGAUUAUC	868	15609	CAUUCUCCAUAGAUUAUC	868	15627	GAUUAUUAUAGGAAUUG	2519
15627	CUUUCUGAUAGUCCGUG	869	15627	CUUUCUGAUAGUCCGUG	869	15645	CAACGGCAUUAUAGAAAG	2520
15645	GUGUGCUUAUACAGUUAACU	870	15645	GUGUGCUUAUACAGUUAACU	870	15663	AGUUAUUAUUAUAGCACAC	2521
15663	UAUGCGGCUAAGGUUAUAG	871	15663	UAUGCGGCUAAGGUUAUAG	871	15681	CUAAACCUUAGAGCGCAUA	2522
15681	GUAGCGGCUAAGGUUAUAG	872	15681	GUAGCGGCUAAGGUUAUAG	872	15699	AGUUAUUAUUAUUAUUA	2523
15699	UUAUAGGCGAUUAUUAUUA	873	15699	UUAUAGGCGAUUAUUAUUA	873	15717	AAUAAAGAACUGCCUUAUA	2524
15717	UAUAAAUUAUUAUUAUUA	874	15717	UAUAAAUUAUUAUUAUUA	874	15735	UGAACACAUUAUUAUUA	2525
15735	AUGUCUGAGGCAUUAUUAU	875	15735	AUGUCUGAGGCAUUAUUAU	875	15753	AAUUAUUAUUAUUAUUA	2526
15753	UGGACUGAGACUGACCUUA	876	15753	UGGACUGAGACUGACCUUA	876	15771	UAAGGUCAGUCUUAUUA	2527

(400/110\_US)

15771	ACUAAAGGACCUACGAAU	877	15771	ACUAAAGGACCUACGAAU	877	15789	AUUCGUGAGGUCUUAUAGU	2528
15789	UUUUGUCACACGACAA	878	15789	UUUUGUCACACGACAA	878	15807	UUGUAGCUGUGAGCAAAA	2529
15807	UUGCUAGUAAACAGGAG	879	15807	UUUUGCUAGUAAACAGGAG	879	15825	CUCUUGUUUAACUAGCAU	2530
15825	GAUGUAGUAAACAGGAG	880	15825	GAUGUAGUAAACAGGAG	880	15843	GCAGUACACGUAUUAUAG	2531
15843	CCUACCCAGUACCAUAA	881	15843	CCUACCCAGUACCAUAA	881	15861	UUGUAGGACGUGGUAAGG	2532
15861	AGAAUUAJAGGCGAGGCU	882	15861	AGAAUUAJAGGCGAGGCU	882	15879	AGCGUGGCUUAUUAUUCU	2533
15879	UUGUUGUGUGAUUAUUG	883	15879	UUGUUGUGUGAUUAUUG	883	15897	CAUAUUAUUAUUAUUAUUA	2534
15897	GUCAAAACAGUAGUACAC	884	15897	GUCAAAACAGUAGUACAC	884	15915	GUGUACCAUCUGUUAUAG	2535
15915	CUUAUGAUUAAGGUGUUG	885	15915	CUUAUGAUUAAGGUGUUG	885	15933	CGAACCUUAUUAUUAUUA	2536
15933	GUGUACUGGCUUAUUAUG	886	15933	GUGUACUGGCUUAUUAUG	886	15951	CAUAUUAUUAUUAUUAUUA	2537
15951	GCUAACCCACUUAUUAUUA	887	15951	GCUAACCCACUUAUUAUUA	887	15969	GUUUGUUAAGGUGGUAAGC	2538
15969	CAUCUUAUUAUUAUUAUUA	888	15969	CAUCUUAUUAUUAUUAUUA	888	15987	CAUACUCCUGAUUAUUAUUA	2539
15987	GCUGAUGUGUUAUUAUUAUUA	889	15987	GCUGAUGUGUUAUUAUUAUUA	889	16005	ACAAGUGAAAGACAUACAGC	2540
16005	UAUUAUUAUUAUUAUUAUUA	890	16005	UAUUAUUAUUAUUAUUAUUA	890	16023	UUCUAAUUAUUAUUAUUAUUA	2541
16023	AAGUUAUUAUUAUUAUUAUUA	891	16023	AAGUUAUUAUUAUUAUUAUUA	891	16041	UAAGCUUAUUAUUAUUAUUA	2542
16041	ACUGGCAUUAUUAUUAUUAUUA	892	16041	ACUGGCAUUAUUAUUAUUAUUA	892	16059	UUGCAACAUUAUUAUUAUUA	2543
16059	AUGUAUUAUUAUUAUUAUUAUUA	893	16059	AUGUAUUAUUAUUAUUAUUAUUA	893	16077	UUAAGCUUAUUAUUAUUAUUA	2544
16077	ACUUAUUAUUAUUAUUAUUAUUA	894	16077	ACUUAUUAUUAUUAUUAUUAUUA	894	16095	GUGAGGUGUUAUUAUUAUUA	2545
16095	CGGUACUGGGAUUAUUAUUAUUA	895	16095	CGGUACUGGGAUUAUUAUUAUUA	895	16113	ACUAGGUGUUAUUAUUAUUA	2546
16113	UUUAUUAUUAUUAUUAUUAUUA	896	16113	UUUAUUAUUAUUAUUAUUAUUA	896	16131	UGUACAUUAUUAUUAUUAUUA	2547
16131	ACUUAUUAUUAUUAUUAUUAUUA	897	16131	ACUUAUUAUUAUUAUUAUUAUUA	897	16149	GCAAGCUUAUUAUUAUUAUUA	2548
16149	CAGGCUUAUUAUUAUUAUUAUUA	898	16149	CAGGCUUAUUAUUAUUAUUAUUA	898	16167	CACAAGCUUAUUAUUAUUAUUA	2549
16167	GUUAUUAUUAUUAUUAUUAUUA	899	16167	GUUAUUAUUAUUAUUAUUAUUA	899	16185	UCUGUUAUUAUUAUUAUUAUUA	2550
16185	ACUUAUUAUUAUUAUUAUUAUUA	900	16185	ACUUAUUAUUAUUAUUAUUAUUA	900	16203	CACCGCAUUAUUAUUAUUAUUA	2551
16203	CCUUAUUAUUAUUAUUAUUAUUA	901	16203	CCUUAUUAUUAUUAUUAUUAUUA	901	16221	AUGGUGUUAUUAUUAUUAUUA	2552
16221	UCCUUAUUAUUAUUAUUAUUAUUA	902	16221	UCCUUAUUAUUAUUAUUAUUAUUA	902	16239	AGCAGUUAUUAUUAUUAUUAUUA	2553
16239	UGCUUAUUAUUAUUAUUAUUAUUA	903	16239	UGCUUAUUAUUAUUAUUAUUAUUA	903	16257	AAUAGCUUAUUAUUAUUAUUA	2554
16257	UCAACUUAUUAUUAUUAUUAUUA	904	16257	UCAACUUAUUAUUAUUAUUAUUA	904	16275	CUAUAUUAUUAUUAUUAUUAUUA	2555
16275	GUGUUAUUAUUAUUAUUAUUAUUA	905	16275	GUGUUAUUAUUAUUAUUAUUAUUA	905	16293	AGGCUUAUUAUUAUUAUUAUUA	2556
16293	UAUUAUUAUUAUUAUUAUUAUUA	906	16293	UAUUAUUAUUAUUAUUAUUAUUA	906	16311	CUGGCUUAUUAUUAUUAUUAUUA	2557
16311	GGUUAUUAUUAUUAUUAUUAUUA	907	16311	GGUUAUUAUUAUUAUUAUUAUUA	907	16329	CAUCAGUUAUUAUUAUUAUUAUUA	2558
16329	GUGACAUUAUUAUUAUUAUUAUUA	908	16329	GUGACAUUAUUAUUAUUAUUAUUA	908	16347	CUAGAUUAUUAUUAUUAUUAUUA	2559
16347	GGAGUUAUUAUUAUUAUUAUUAUUA	909	16347	GGAGUUAUUAUUAUUAUUAUUAUUA	909	16365	AUAUAUUAUUAUUAUUAUUAUUA	2560
16365	UGCAUUAUUAUUAUUAUUAUUAUUA	910	16365	UGCAUUAUUAUUAUUAUUAUUAUUA	910	16383	GAGGCUUAUUAUUAUUAUUAUUA	2561
16383	CCCAUUAUUAUUAUUAUUAUUAUUA	911	16383	CCCAUUAUUAUUAUUAUUAUUAUUA	911	16401	AUAUUAUUAUUAUUAUUAUUAUUA	2562
16401	UUGCUUAUUAUUAUUAUUAUUAUUA	912	16401	UUGCUUAUUAUUAUUAUUAUUAUUA	912	16419	AAUUAUUAUUAUUAUUAUUAUUA	2563
16419	UUUGCUUAUUAUUAUUAUUAUUAUUA	913	16419	UUUGCUUAUUAUUAUUAUUAUUAUUA	913	16437	UGUUAUUAUUAUUAUUAUUAUUA	2564
16437	AAUUAUUAUUAUUAUUAUUAUUAUUA	914	16437	AAUUAUUAUUAUUAUUAUUAUUAUUA	914	16455	GUUUAUUAUUAUUAUUAUUAUUA	2565
16455	CAUUAUUAUUAUUAUUAUUAUUAUUA	915	16455	CAUUAUUAUUAUUAUUAUUAUUAUUA	915	16473	CAUUAUUAUUAUUAUUAUUAUUA	2566
16473	CGCAUUAUUAUUAUUAUUAUUAUUA	916	16473	CGCAUUAUUAUUAUUAUUAUUAUUA	916	16491	AAUUAUUAUUAUUAUUAUUAUUA	2567
16491	UGGCUUAUUAUUAUUAUUAUUAUUA	917	16491	UGGCUUAUUAUUAUUAUUAUUAUUA	917	16509	AAUUAUUAUUAUUAUUAUUAUUA	2568
16509	UACAUUAUUAUUAUUAUUAUUAUUA	918	16509	UACAUUAUUAUUAUUAUUAUUAUUA	918	16527	AAGUUAUUAUUAUUAUUAUUAUUA	2569

(400/110\_US)

16527	UGUACUGAGAGACUCAGC	819	16527	UGUACUGAGAGACUCAGC	919	16545	GCUUGAGUCUCUACAGUACA	2570
16545	CUUUUGCGAGAGAAACGC	920	16545	CUUUUGCGAGAGAAACGC	920	16563	GCGUUCUGCUGCGAAAG	2571
16563	CUCAAAGCCACUGAGGAAA	921	16563	CUCAAAGCCACUGAGGAAA	921	16581	UUUCCUCAGUGGCUUUGAG	2572
16581	ACAUUUAAGCUGUCAUUG	922	16581	ACAUUUAAGCUGUCAUUG	922	16599	CAUUGACAGCUUAAUUG	2573
16599	GGUUAUUGCCACUGUACGCG	923	16599	GGUUAUUGCCACUGUACGCG	923	16617	CGCGUACAGUGGCAUUAAC	2574
16617	GAAGUACUCUCUGACAGAG	924	16617	GAAGUACUCUCUGACAGAG	924	16635	CUCUGACAGAGUACUUC	2575
16635	GAUUGCAUCUUAUUGG	925	16635	GAUUGCAUCUUAUUGG	925	16653	CCUUGAAAGAUCAUUC	2576
16653	GAGGUUGGAAACCUAGAC	926	16653	GAGGUUGGAAACCUAGAC	926	16671	GUCUAGGUUUUCCAAACCUC	2577
16671	CCACCAUUGAACAGAAACU	927	16671	CCACCAUUGAACAGAAACU	927	16689	AGUUCUGUUAUUGGUGG	2578
16689	UAUGUCUUUACUGGUUACC	928	16689	UAUGUCUUUACUGGUUACC	928	16707	GGUAAACCAUUAAGACUA	2579
16707	CGUGUAACUAAAUUAGUA	929	16707	CGUGUAACUAAAUUAGUA	929	16725	UACUAAUUAUUAUACACG	2580
16725	AAAGUACAGAUUGGAGAGU	930	16725	AAAGUACAGAUUGGAGAGU	930	16743	ACUCUCCAAUCUGUACUUU	2581
16743	UACACCUUUGAAAGGUG	931	16743	UACACCUUUGAAAGGUG	931	16761	CACCUUUUCAAAGGUGUA	2582
16761	GACUUGGUGAGUGUGUUG	932	16761	GACUUGGUGAGUGUGUUG	932	16779	CAACAGCAUCCACUAGUC	2583
16779	GUGUACAGGUGUACACGA	933	16779	GUGUACAGGUGUACACGA	933	16797	UCGUAGUACUCUGUACAC	2584
16797	ACAUACAAGUUAUUGUUG	934	16797	ACAUACAAGUUAUUGUUG	934	16815	CAACAUCAAGUUGUAGU	2585
16815	GGUGAUUACUUUGUGUUGA	935	16815	GGUGAUUACUUUGUGUUGA	935	16833	UCAACACAAAGUUAUACAC	2586
16833	ACAUCACACUGUUAUUGC	936	16833	ACAUCACACUGUUAUUGC	936	16851	GCAUUAACAGUGUGAGUUG	2587
16851	CCACUUAUGUGCACCUACUC	937	16851	CCACUUAUGUGCACCUACUC	937	16869	GAGUAGGUGCACUAAUGG	2588
16869	CUAGUGCCACAGACACU	938	16869	CUAGUGCCACAGACACU	938	16887	AGUGCUCUUGUGGACUAG	2589
16887	UAUGUGAGAAUUAUUGGCU	939	16887	UAUGUGAGAAUUAUUGGCU	939	16905	AGCCAGUAAUUCUCACAU	2590
16905	UUGUACCCAAACACUACA	940	16905	UUGUACCCAAACACUACA	940	16923	UGUUGAGUGUUGGUGUACA	2591
16923	AUCUCAGAGUUAUUCUA	941	16923	AUCUCAGAGUUAUUCUA	941	16941	UAGAAACUACUCUGAGAU	2592
16941	AGCAAUUGGCAAUUAUC	942	16941	AGCAAUUGGCAAUUAUC	942	16959	GAUAAUUGCAACAUUGCU	2593
16959	CAAAAGGUGCGCAUGCAA	943	16959	CAAAAGGUGCGCAUGCAA	943	16977	UUUGCAUGCCGACCUUUG	2594
16977	AAGUACUCUACACUCCAA	944	16977	AAGUACUCUACACUCCAA	944	16995	CUUGGAGUGUAGAGUACU	2595
16995	GGACCACCUUGUACUGGUA	945	16995	GGACCACCUUGUACUGGUA	945	17013	UACCAGUACCGGUGGUGC	2596
17013	AAGAGUCUUUUGCCAUUC	946	17013	AAGAGUCUUUUGCCAUUC	946	17031	CGAUGGCAAAUUGACUCUU	2597
17031	GGACUUGCUCUUAUUAAC	947	17031	GGACUUGCUCUUAUUAAC	947	17049	GGUAAUAGAGAGCAAGUCC	2598
17049	CCAUUCUGCGCAUAGUGU	948	17049	CCAUUCUGCGCAUAGUGU	948	17067	ACACUAGCGAGCAGAUUG	2599
17067	UAUACGGCAUGCUCUACUG	949	17067	UAUACGGCAUGCUCUACUG	949	17085	CAUGAGAGCAUGCCGUUA	2600
17085	GCAGCUGUUGAUGCCUUA	950	17085	GCAGCUGUUGAUGCCUUA	950	17103	AUAGGCAUCAAACAGCUGC	2601
17103	UGUGAAAAGGCAUUAUAAU	951	17103	UGUGAAAAGGCAUUAUAAU	951	17121	AUUUAAUGCCUUUUUACA	2602
17121	UAUUUGCCCAUAGAUAAU	952	17121	UAUUUGCCCAUAGAUAAU	952	17139	AUUUAUCUAGGGCAAAUA	2603
17139	UGUAGUAGAAUUAUUAU	953	17139	UGUAGUAGAAUUAUUAU	953	17157	CAGGUAGAUUUAUUAUUA	2604
17157	GCAGCUGCGCGUAGAGU	954	17157	GCAGCUGCGCGUAGAGU	954	17175	ACUCUACCGCGCAGCAGC	2605
17175	UGUUUUGAUAAUUAUUA	955	17175	UGUUUUGAUAAUUAUUA	955	17193	CUUUGAAUUAUUAUUAUUA	2606
17193	GAUAAUUAACACUAGAAC	956	17193	GAUAAUUAACACUAGAAC	956	17211	GUUGUAGUUGUUAUUAUUA	2607
17211	CAGUAAUUAUUAUUAUUA	957	17211	CAGUAAUUAUUAUUAUUA	957	17229	CAGUCAGAAACAUUAUUA	2608
17229	GUAAUUGCAUUAUUAUUA	958	17229	GUAAUUGCAUUAUUAUUA	958	17247	UUUCUGGCAUUAUUAUUA	2609
17247	ACAACUGCUGACAUUAUUA	959	17247	ACAACUGCUGACAUUAUUA	959	17265	CUACAACUGCAGCAGUUAU	2610
17265	GUCUUUGAUGAAUUAUUA	960	17265	GUCUUUGAUGAAUUAUUA	960	17283	UAGAGAUUAUUAUUAUUA	2611



(400/110\_US)

17283	AUGGCUACUAAUUAUGACU	961	17283	AUGGCUACUAAUUAUGACU	961	17301	AGUCAUUAUAGUAGCCAU	2612
17301	UUGAGUGUUGUCAAUAGCUA	962	17301	UUGAGUGUUGUCAAUAGCUA	962	17319	UAGCAUUGAACACACUCAA	2613
17319	AGACUUGUGUCAAUAGCUA	963	17319	AGACUUGUGUCAAUAGCUA	963	17337	AGUUAUUGAACGAAAGUCU	2614
17337	UACGUCUUAUUGGCGAUC	964	17337	UACGUCUUAUUGGCGAUC	964	17355	GAUCGCAUUAUAGACGUA	2615
17355	CCUGUCUAAUUAACGAGCC	965	17355	CCUGUCUAAUUAACGAGCC	965	17373	GGGUGGUAUUAUAGACGAG	2616
17373	CCCGCACAUUGGCGACUA	966	17373	CCCGCACAUUGGCGACUA	966	17391	UAGUCAGCAUUGUGCGGGG	2617
17391	AAAGGCACUUAAGAACAG	967	17391	AAAGGCACUUAAGAACAG	967	17409	CUGGUUUAUUAUAGCCUUU	2618
17409	GAUAUUAUUAUUAUAGUGU	968	17409	GAUAUUAUUAUUAUAGUGU	968	17427	ACACUGAAUUAUUAUUAUUC	2619
17427	UGCAGACUUAUUAUUAUUA	969	17427	UGCAGACUUAUUAUUAUUA	969	17445	UUGUUUUAUUAUUAUUAUUC	2620
17445	UAAGGUCCAGACUUAUUAU	970	17445	UAAGGUCCAGACUUAUUAU	970	17463	GGAACAUGUUGGACCUUAU	2621
17463	CUUGGAACUUAUUAUUAUUA	971	17463	CUUGGAACUUAUUAUUAUUA	971	17481	AACGGCAGCAUUAUUAUUA	2622
17481	UGUCCUGGAAUUAUUAUUA	972	17481	UGUCCUGGAAUUAUUAUUA	972	17499	CAACAUAUUAUUAUUAUUA	2623
17499	GACACUGGAGUUAUUAUUA	973	17499	GACACUGGAGUUAUUAUUA	973	17517	CUAAGCACUUAUUAUUAUUA	2624
17517	GUUAUUAUUAUUAUUAUUA	974	17517	GUUAUUAUUAUUAUUAUUA	974	17535	UUAAGCUUAUUAUUAUUAUUA	2625
17535	AAAGCACACUUAUUAUUAUUA	975	17535	AAAGCACACUUAUUAUUAUUA	975	17553	ACUUAUUAUUAUUAUUAUUA	2626
17553	UCAGCUUAUUAUUAUUAUUA	976	17553	UCAGCUUAUUAUUAUUAUUA	976	17571	UUUUAUUAUUAUUAUUAUUA	2627
17571	AUUAUUAUUAUUAUUAUUA	977	17571	AUUAUUAUUAUUAUUAUUA	977	17589	UAACACCUUAUUAUUAUUAUUA	2628
17589	UAUUAUUAUUAUUAUUAUUA	978	17589	UAUUAUUAUUAUUAUUAUUA	978	17607	AUGAAUUAUUAUUAUUAUUA	2629
17607	UCUGCAUUAUUAUUAUUAUUA	979	17607	UCUGCAUUAUUAUUAUUAUUA	979	17625	GAGGUUAUUAUUAUUAUUAUUA	2630
17625	CAUUAUUAUUAUUAUUAUUA	980	17625	CAUUAUUAUUAUUAUUAUUA	980	17643	CUCUUAUUAUUAUUAUUAUUA	2631
17643	GAUUAUUAUUAUUAUUAUUA	981	17643	GAUUAUUAUUAUUAUUAUUA	981	17661	GAUUGGUAUUAUUAUUAUUA	2632
17661	CCUGCUUAUUAUUAUUAUUA	982	17661	CCUGCUUAUUAUUAUUAUUA	982	17679	CAGCUUAUUAUUAUUAUUAUUA	2633
17679	GUUUAUUAUUAUUAUUAUUA	983	17679	GUUUAUUAUUAUUAUUAUUA	983	17697	UAUUAUUAUUAUUAUUAUUA	2634
17697	AUUAUUAUUAUUAUUAUUA	984	17697	AUUAUUAUUAUUAUUAUUA	984	17715	CUACAGCUUAUUAUUAUUAUUA	2635
17715	GUUUAUUAUUAUUAUUAUUA	985	17715	GUUUAUUAUUAUUAUUAUUA	985	17733	AUCCUUAUUAUUAUUAUUAUUA	2636
17733	UUGCUUAUUAUUAUUAUUAUUA	986	17733	UUGCUUAUUAUUAUUAUUAUUA	986	17751	CAACAGCUUAUUAUUAUUAUUA	2637
17751	GAUUAUUAUUAUUAUUAUUA	987	17751	GAUUAUUAUUAUUAUUAUUA	987	17769	CAGAACCUGUUAUUAUUAUUA	2638
17769	GAUUAUUAUUAUUAUUAUUA	988	17769	GAUUAUUAUUAUUAUUAUUA	988	17787	AUAUUAUUAUUAUUAUUAUUA	2639
17787	UUAUUAUUAUUAUUAUUAUUA	989	17787	UUAUUAUUAUUAUUAUUAUUA	989	17805	UUUUAUUAUUAUUAUUAUUA	2640
17805	ACAGCACUUAUUAUUAUUAUUA	990	17805	ACAGCACUUAUUAUUAUUAUUA	990	17823	CAUUAUUAUUAUUAUUAUUA	2641
17823	GUCAACGCUUAUUAUUAUUAUUA	991	17823	GUCAACGCUUAUUAUUAUUAUUA	991	17841	CCACAUAUUAUUAUUAUUAUUA	2642
17841	GUUAUUAUUAUUAUUAUUAUUA	992	17841	GUUAUUAUUAUUAUUAUUAUUA	992	17859	UUUUAUUAUUAUUAUUAUUA	2643
17859	AUUGGCUUAUUAUUAUUAUUA	993	17859	AUUGGCUUAUUAUUAUUAUUA	993	17877	UAUUAUUAUUAUUAUUAUUA	2644
17877	AUGUCUUAUUAUUAUUAUUAUUA	994	17877	AUGUCUUAUUAUUAUUAUUAUUA	994	17895	AAAGUUAUUAUUAUUAUUAUUA	2645
17895	UAUUAUUAUUAUUAUUAUUAUUA	995	17895	UAUUAUUAUUAUUAUUAUUAUUA	995	17913	UAAUUAUUAUUAUUAUUAUUA	2646
17913	ACAAGUUAUUAUUAUUAUUAUUA	996	17913	ACAAGUUAUUAUUAUUAUUAUUA	996	17931	GUGGUUAUUAUUAUUAUUAUUA	2647
17931	CGUGCAUUAUUAUUAUUAUUAUUA	997	17931	CGUGCAUUAUUAUUAUUAUUAUUA	997	17949	AUGUUAUUAUUAUUAUUAUUA	2648
17949	UAUUAUUAUUAUUAUUAUUAUUA	998	17949	UAUUAUUAUUAUUAUUAUUAUUA	998	17967	UUUAUUAUUAUUAUUAUUAUUA	2649
17967	ACUGGCUUAUUAUUAUUAUUAUUA	999	17967	ACUGGCUUAUUAUUAUUAUUAUUA	999	17985	AGUUAUUAUUAUUAUUAUUAUUA	2650
17985	UGUUAUUAUUAUUAUUAUUAUUA	1000	17985	UGUUAUUAUUAUUAUUAUUAUUA	1000	18003	CAGUUAUUAUUAUUAUUAUUA	2651
18003	GGUUAUUAUUAUUAUUAUUAUUA	1001	18003	GGUUAUUAUUAUUAUUAUUAUUA	1001	18021	CCUGUUAUUAUUAUUAUUAUUA	2652
18021	GCACCUUAUUAUUAUUAUUAUUA	1002	18021	GCACCUUAUUAUUAUUAUUAUUA	1002	18039	CGCUGUUAUUAUUAUUAUUAUUA	2653

18039	GIUGAUUAUAAAGUUAACAAGA	1003	18039	GIUGAUUAUAAAGUUAACAAGA	1003	18057	UCUUGAAACUUUAUAUUAACAAC	2654
18057	ACUGAAGGAUUAUGUGUUG	1004	18057	ACUGAAGGAUUAUGUGUUG	1004	18075	CAACACAUAAUCCUUAUGU	2655
18075	GACUAUACGAGCAUACCAA	1005	18075	GACUAUACGAGCAUACCAA	1005	18093	UUGGUUAUGCCUGGUUAUGU	2656
18093	AAGGACAUAGCCUUAACCGUA	1006	18093	AAGGACAUAGCCUUAACCGUA	1006	18111	UAGGUAUGGUCAUGUCCU	2657
18111	AGACUAUCUCUAUGAUGG	1007	18111	AGACUAUCUCUAUGAUGG	1007	18129	CCAUAUGAGAGUAUGAGUCU	2658
18129	GGUUAUCAAUUGAAUUAACC	1008	18129	GGUUAUCAAUUGAAUUAACC	1008	18147	GGUAUUAUUAUUGAAUUAACC	2659
18147	CAAGUCUAUUGUUAUUAACC	1009	18147	CAAGUCUAUUGUUAUUAACC	1009	18165	UAGGUAUUAUUAUUAUUAACC	2660
18165	AAUUGUUAUUAUUAUUAACC	1010	18165	AAUUGUUAUUAUUAUUAACC	1010	18183	CGGUGUAUUAUUAUUAUUAACC	2661
18183	GAAGAAGCUUAUUAUUAACC	1011	18183	GAAGAAGCUUAUUAUUAACC	1011	18201	CGGUGUAUUAUUAUUAUUAACC	2662
18201	GUUGUGUGUGUUAUUAUUAACC	1012	18201	GUUGUGUGUGUUAUUAUUAACC	1012	18219	AGCCAUAUUAUUAUUAUUAACC	2663
18219	UUUGUGUGUGUUAUUAUUAACC	1013	18219	UUUGUGUGUGUUAUUAUUAACC	1013	18237	GACAGCCUUAUUAUUAUUAACC	2664
18237	CAUGCAUUAUUAUUAUUAACC	1014	18237	CAUGCAUUAUUAUUAUUAACC	1014	18255	GAGUAUUAUUAUUAUUAUUAACC	2665
18255	GUGGUAUUAUUAUUAUUAACC	1015	18255	GUGGUAUUAUUAUUAUUAACC	1015	18273	CAGGUAUUAUUAUUAUUAUUAACC	2666
18273	CUCAGUAUUAUUAUUAUUAACC	1016	18273	CUCAGUAUUAUUAUUAUUAACC	1016	18291	UAGAUAUUAUUAUUAUUAUUAACC	2667
18291	ACAGGUAUUAUUAUUAUUAACC	1017	18291	ACAGGUAUUAUUAUUAUUAACC	1017	18309	CUAUAUUAUUAUUAUUAUUAACC	2668
18309	GCUGUAUUAUUAUUAUUAACC	1018	18309	GCUGUAUUAUUAUUAUUAACC	1018	18327	CAUAUAUUAUUAUUAUUAUUAACC	2669
18327	GUUGUAUUAUUAUUAUUAACC	1019	18327	GUUGUAUUAUUAUUAUUAACC	1019	18345	UUAUAUUAUUAUUAUUAUUAACC	2670
18345	ACAGUAUUAUUAUUAUUAACC	1020	18345	ACAGUAUUAUUAUUAUUAACC	1020	18363	UUAUAUUAUUAUUAUUAUUAACC	2671
18363	AAUGUAUUAUUAUUAUUAACC	1021	18363	AAUGUAUUAUUAUUAUUAACC	1021	18381	CUUGGUAUUAUUAUUAUUAUUAACC	2672
18381	GGUGUAUUAUUAUUAUUAACC	1022	18381	GGUGUAUUAUUAUUAUUAACC	1022	18399	GAUGUAUUAUUAUUAUUAUUAACC	2673
18399	CUUAUAUUAUUAUUAUUAACC	1023	18399	CUUAUAUUAUUAUUAUUAACC	1023	18417	UAUAUAUUAUUAUUAUUAUUAACC	2674
18417	AAUGUAUUAUUAUUAUUAACC	1024	18417	AAUGUAUUAUUAUUAUUAACC	1024	18435	CUUAUAUUAUUAUUAUUAUUAACC	2675
18435	GUUGUAUUAUUAUUAUUAACC	1025	18435	GUUGUAUUAUUAUUAUUAACC	1025	18453	CUUAUAUUAUUAUUAUUAUUAACC	2676
18453	GUUGUAUUAUUAUUAUUAACC	1026	18453	GUUGUAUUAUUAUUAUUAACC	1026	18471	UAUAUAUUAUUAUUAUUAUUAACC	2677
18471	ACUGUAUUAUUAUUAUUAACC	1027	18471	ACUGUAUUAUUAUUAUUAACC	1027	18489	CUUAUAUUAUUAUUAUUAUUAACC	2678
18489	GACAGUAUUAUUAUUAUUAACC	1028	18489	GACAGUAUUAUUAUUAUUAACC	1028	18507	GAUGUAUUAUUAUUAUUAUUAACC	2679
18507	CUUGGUAUUAUUAUUAUUAACC	1029	18507	CUUGGUAUUAUUAUUAUUAACC	1029	18525	CAAGUAUUAUUAUUAUUAUUAACC	2680
18525	GAGUAUUAUUAUUAUUAUUAACC	1030	18525	GAGUAUUAUUAUUAUUAUUAACC	1030	18543	CUUAUAUUAUUAUUAUUAUUAACC	2681
18543	UUAUAUUAUUAUUAUUAUUAACC	1031	18543	UUAUAUUAUUAUUAUUAUUAACC	1031	18561	GUUAUAUUAUUAUUAUUAUUAACC	2682
18561	CUUGUAUUAUUAUUAUUAUUAACC	1032	18561	CUUGUAUUAUUAUUAUUAUUAACC	1032	18579	GAUGUAUUAUUAUUAUUAUUAACC	2683
18579	CUUGUAUUAUUAUUAUUAUUAACC	1033	18579	CUUGUAUUAUUAUUAUUAUUAACC	1033	18597	GAUGUAUUAUUAUUAUUAUUAACC	2684
18597	CUUGUAUUAUUAUUAUUAUUAACC	1034	18597	CUUGUAUUAUUAUUAUUAUUAACC	1034	18615	GAUGUAUUAUUAUUAUUAUUAACC	2685
18615	CUUGUAUUAUUAUUAUUAUUAACC	1035	18615	CUUGUAUUAUUAUUAUUAUUAACC	1035	18633	GAUGUAUUAUUAUUAUUAUUAACC	2686
18633	CUUGUAUUAUUAUUAUUAUUAACC	1036	18633	CUUGUAUUAUUAUUAUUAUUAACC	1036	18651	GAUGUAUUAUUAUUAUUAUUAACC	2687
18651	CUUGUAUUAUUAUUAUUAUUAACC	1037	18651	CUUGUAUUAUUAUUAUUAUUAACC	1037	18669	GAUGUAUUAUUAUUAUUAUUAACC	2688
18669	CUUGUAUUAUUAUUAUUAUUAACC	1038	18669	CUUGUAUUAUUAUUAUUAUUAACC	1038	18687	GAUGUAUUAUUAUUAUUAUUAACC	2689

(400/110\_US)

18795	GCAGUCCAUAGAGUGCUUUG	1045	18795	GCAGUCCAUAGAGUGCUUUG	1045	18813	CAAGCAGUUAUGGACUGC	2696
18813	GUUAGCGGUUGAUUGGU	1046	18813	GUUAGCGGUUGAUUGGU	1046	18831	ACCAUCAAAGCGCUUAC	2697
18831	UCUGUAGAUACCCUUAU	1047	18831	UCUGUAGAUACCCUUAU	1047	18849	UAAUAGGUAUUAUACAGA	2698
18849	AUAGGAGUAACUAGGAG	1048	18849	AUAGGAGUAACUAGGAG	1048	18867	CCUCAGUUAUUAUCCUUAU	2699
18867	GUUAGUUGUUGUAGGAA	1049	18867	GUUAGUUGUUGUAGGAA	1049	18885	UUCUGCAAGCAGAAUUAAC	2700
18885	AAAGUACAAACAUUGGU	1050	18885	AAAGUACAAACAUUGGU	1050	18903	CAACCAUGUGUUGUACUUA	2701
18903	GUGAAGUCUAGUUGCUUG	1051	18903	GUGAAGUCUAGUUGCUUG	1051	18921	CAAGCAUAGCAGUUAUAC	2702
18921	GUUAGUAGUUAUCCAGUUC	1052	18921	GUUAGUAGUUAUCCAGUUC	1052	18939	GAAGUAGAAUUAUUAUAC	2703
18939	CUUACAGUUAUUGGAAUUC	1053	18939	CUUACAGUUAUUGGAAUUC	1053	18957	GAUUAUCCAAUUGUUAUAG	2704
18957	CCAAAGGCUUAUUAUUG	1054	18957	CCAAAGGCUUAUUAUUG	1054	18975	CACAUUAGUAGCCUUGG	2705
18975	GUGCCUAGGCUUAUUAU	1055	18975	GUGCCUAGGCUUAUUAU	1055	18993	CUACUUCAGCCUGAGGAC	2706
18993	GAUUGGAAGUUAUUAU	1056	18993	GAUUGGAAGUUAUUAU	1056	19011	UUGCAGUAGAAUUAUUAU	2707
19011	GCUCAGCCAUUAUUAU	1057	19011	GCUCAGCCAUUAUUAU	1057	19029	UGUCACUUAUUAUUAU	2708
19029	AAAGCUUAUUAUUAU	1058	19029	AAAGCUUAUUAUUAU	1058	19047	CCUCUUAUUAUUAUUAU	2709
19047	GAACUCUUAUUAUUAU	1059	19047	GAACUCUUAUUAUUAU	1059	19065	CAUUAAGAUUAUUAUUAU	2710
19065	GUACACUUAUUAUUAU	1060	19065	GUACACUUAUUAUUAU	1060	19083	AUUUAUCGUAUUAUUAU	2711
19083	UUCACUUAUUAUUAU	1061	19083	UUCACUUAUUAUUAU	1061	19101	AUUAUUAUUAUUAUUAU	2712
19101	UUGUUAUUAUUAUUAU	1062	19101	UUGUUAUUAUUAUUAU	1062	19119	CGUUAUUAUUAUUAUUAU	2713
19119	GUUAGUUAUUAUUAU	1063	19119	GUUAGUUAUUAUUAU	1063	19137	UGGCUUAUUAUUAUUAU	2714
19137	AUUGAAUUAUUAUUAU	1064	19137	AUUGAAUUAUUAUUAU	1064	19155	ACUUAUUAUUAUUAUUAU	2715
19155	UUGACAAUUAUUAUUAU	1065	19155	UUGACAAUUAUUAUUAU	1065	19173	ACUUAUUAUUAUUAUUAU	2716
19173	UUAUUAUUAUUAUUAU	1066	19173	UUAUUAUUAUUAUUAU	1066	19191	CUUGUUAUUAUUAUUAU	2717
19191	GGCUUAUUAUUAUUAU	1067	19191	GGCUUAUUAUUAUUAU	1067	19209	AACUUAUUAUUAUUAUUAU	2718
19209	UUGUUAUUAUUAUUAU	1068	19209	UUGUUAUUAUUAUUAU	1068	19227	CAUGCUUAUUAUUAUUAU	2719
19227	GCAUUAUUAUUAUUAU	1069	19227	GCAUUAUUAUUAUUAU	1069	19245	AAGUUAUUAUUAUUAUUAU	2720
19245	UUCGAAUUAUUAUUAU	1070	19245	UUCGAAUUAUUAUUAU	1070	19263	UAAUUAUUAUUAUUAUUAU	2721
19263	ACUUAUUAUUAUUAUUAU	1071	19263	ACUUAUUAUUAUUAUUAU	1071	19281	GCAUUAUUAUUAUUAUUAU	2722
19281	CCUUAUUAUUAUUAUUAU	1072	19281	CCUUAUUAUUAUUAUUAU	1072	19299	CAGAAUUAUUAUUAUUAU	2723
19299	GAUUAUUAUUAUUAUUAU	1073	19299	GAUUAUUAUUAUUAUUAU	1073	19317	GAGCUUAUUAUUAUUAUUAU	2724
19317	CAUGGAAUUAUUAUUAU	1074	19317	CAUGGAAUUAUUAUUAU	1074	19335	ACUUAUUAUUAUUAUUAU	2725
19335	UCGAAUUAUUAUUAUUAU	1075	19335	UCGAAUUAUUAUUAUUAU	1075	19353	GAACAUAUUAUUAUUAUUAU	2726
19353	CCACUUAUUAUUAUUAU	1076	19353	CCACUUAUUAUUAUUAU	1076	19371	ACGUAUUAUUAUUAUUAU	2727
19371	UGUUAUUAUUAUUAUUAU	1077	19371	UGUUAUUAUUAUUAUUAU	1077	19389	AUUAUUAUUAUUAUUAUUAU	2728
19389	UAAGUUAUUAUUAUUAU	1078	19389	UAAGUUAUUAUUAUUAU	1078	19407	UGCAAUUAUUAUUAUUAU	2729
19407	AGACUUAUUAUUAUUAU	1079	19407	AGACUUAUUAUUAUUAU	1079	19425	ACUUAUUAUUAUUAUUAU	2730
19425	UACGAAUUAUUAUUAU	1080	19425	UACGAAUUAUUAUUAU	1080	19443	CAUUAUUAUUAUUAUUAU	2731
19443	GCAUUAUUAUUAUUAUUAU	1081	19443	GCAUUAUUAUUAUUAUUAU	1081	19461	AAUUAUUAUUAUUAUUAU	2732
19461	UCUGUUAUUAUUAUUAU	1082	19461	UCUGUUAUUAUUAUUAU	1082	19479	AUAGGUAUUAUUAUUAUUAU	2733
19479	UGGAAUUAUUAUUAUUAU	1083	19479	UGGAAUUAUUAUUAUUAU	1083	19497	UCCACUUAUUAUUAUUAUUAU	2734
19497	GAUUAUUAUUAUUAUUAU	1084	19497	GAUUAUUAUUAUUAUUAU	1084	19515	GUACUUAUUAUUAUUAUUAU	2735
19515	AAUUAUUAUUAUUAUUAU	1085	19515	AAUUAUUAUUAUUAUUAU	1085	19533	GUACUUAUUAUUAUUAUUAU	2736
19533	CAGAAUUAUUAUUAUUAU	1086	19533	CAGAAUUAUUAUUAUUAU	1086	19551	CCACUUAUUAUUAUUAUUAU	2737



(400/110\_US)

19551	GCUIUAUAUUGUUAUA	1087	19551	GCUIUAUAUUGUUAUA	1087	19569	UAUIUAACAACAUUAUAGC	2738
19569	AAAGGACACUUAUUGGAC	1088	19569	AAAGGACACUUAUUGGAC	1088	19587	GUCCAACAAGUUGUUAU	2739
19587	CAGCGCGGGAAGACCUUG	1089	19587	CAGCGCGGGAAGACCUUG	1089	19605	CAGGUGCUUCGCCGCGUG	2740
19605	GUUCCAUCAUAUAUAUG	1090	19605	GUUCCAUCAUAUAUAUG	1090	19623	CAUUAUAUAUGUAGAAAC	2741
19623	GCUGUUAACACAAAGUAG	1091	19623	GCUGUUAACACAAAGUAG	1091	19641	CUACCUUUGUUAACACAGC	2742
19641	GAUGGUUAUUGUGGAGA	1092	19641	GAUGGUUAUUGUGGAGA	1092	19659	UCUCCACAUAUUAACCAUC	2743
19659	AUCUUUGAAAUAAGACAA	1093	19659	AUCUUUGAAAUAAGACAA	1093	19677	UUGCUUAUUAUUAACGAU	2744
19677	ACAUUCCUGUUAUUGUUG	1094	19677	ACAUUCCUGUUAUUGUUG	1094	19695	CAACUAUAACAGGAAGUGU	2745
19695	GCAUUGGAGUUAUUGGCUA	1095	19695	GCAUUGGAGUUAUUGGCUA	1095	19713	UAGCCCAAGCUCUUAUUGC	2746
19713	AAGCGUAACUAUAACACAG	1096	19713	AAGCGUAACUAUAACACAG	1096	19731	CUGGUUAUAUUGUUAACGCUU	2747
19731	GUGCCAGAGUAUAAGAUAC	1097	19731	GUGCCAGAGUAUAAGAUAC	1097	19749	GUACUUAUAUCUCUGGAC	2748
19749	CUCAAUAUAUUGGUGUUG	1098	19749	CUCAAUAUAUUGGUGUUG	1098	19767	CAACACCAAAUAUUAUGAG	2749
19767	GAUAUGGCUUAUAUAUG	1099	19767	GAUAUGGCUUAUAUAUG	1099	19785	CAGUAUAAGCAGCGAUAC	2750
19785	GUAAUCUGGACUAUAACAA	1100	19785	GUAAUCUGGACUAUAACAA	1100	19803	UIUUGUAGUCCAGAUUAC	2751
19803	AGAGAAGCCCCAGCACAUG	1101	19803	AGAGAAGCCCCAGCACAUG	1101	19821	CAUGUGUGGGGCUUUCUCU	2752
19821	GUUUAUAUAUAGGUGUCU	1102	19821	GUUUAUAUAUAGGUGUCU	1102	19839	UUAUGUAGUCCAGAUUAG	2753
19839	UGCACAAUGACUACAUAUG	1103	19839	UGCACAAUGACUACAUAUG	1103	19857	CAAGUCAGUUAUUGGCA	2754
19857	GCCAAAGAACCUUACUUA	1104	19857	GCCAAAGAACCUUACUUA	1104	19875	UCUCAGUAGGUUUCUUGGC	2755
19875	AGUGCUUUGUUAUUAUA	1105	19875	AGUGCUUUGUUAUUAUA	1105	19893	UAGUGAAGAACCAAGCACU	2756
19893	ACUGUUAUUGUUAUUAUA	1106	19893	ACUGUUAUUGUUAUUAUA	1106	19911	UACCAACAACAAGACAGU	2757
19911	AGAGUGGAGGACAGGUAUG	1107	19911	AGAGUGGAGGACAGGUAUG	1107	19929	CUACCUUCCUCCACUCU	2758
19929	GACCUUUAUUAAGACGCC	1108	19929	GACCUUUAUUAAGACGCC	1108	19947	GGCGUUAUUAUUAAGGUC	2759
19947	CGUUAUGGUGUUAUUAUA	1109	19947	CGUUAUGGUGUUAUUAUA	1109	19965	UIUUAUAACAACCAUUAUG	2760
19965	ACAGAAGGUUUAUUAUA	1110	19965	ACAGAAGGUUUAUUAUA	1110	19983	CUUUGACUGAACCUUUCUGU	2761
19983	GGUCUUAACCUUUAUAAGG	1111	19983	GGUCUUAACCUUUAUAAGG	1111	20001	CCUUGAAGGUGUUAAGAC	2762
20001	GGACCAAGCAGUUAAGG	1112	20001	GGACCAAGCAGUUAAGG	1112	20019	CGCUAGUUGUGUGGUGUCC	2763
20019	GUCAUUGGAGUUAUAUA	1113	20019	GUCAUUGGAGUUAUAUA	1113	20037	UUAUUGUAGUCCAUUAGC	2764
20037	AUUGGAGAAUCAGUAAAA	1114	20037	AUUGGAGAAUCAGUAAAA	1114	20055	UUUUUACUGAUUUCUCCAU	2765
20055	ACACAGUUAUAUAUAUA	1115	20055	ACACAGUUAUAUAUAUA	1115	20073	UAAAGUUAUAUAUAUAUA	2766
20073	AAGAAAGUAGCGGCUUA	1116	20073	AAGAAAGUAGCGGCUUA	1116	20091	UAAUGCGUUAUAUAUAUA	2767
20091	AUUAACAGUUAUAUAUA	1117	20091	AUUAACAGUUAUAUAUA	1117	20109	UUUCAGGCAACUGUUAUA	2768
20109	ACCUUAUAUAUAUAUA	1118	20109	ACCUUAUAUAUAUAUA	1118	20127	UGCUCUGUUAUAUAUAUA	2769
20127	AGAGACUUAUAUAUAUA	1119	20127	AGAGACUUAUAUAUAUA	1119	20145	UAAAUUCCUUAUAUAUA	2770
20145	AAGCCAGUUAUAUAUAUA	1120	20145	AAGCCAGUUAUAUAUAUA	1120	20163	CCAUUUGUUAUAUAUAUA	2771
20163	GAACUGACUUAUAUAUAUA	1121	20163	GAACUGACUUAUAUAUAUA	1121	20181	GCUCGAGAAAGUUAUAUA	2772
20181	CUCGCUUAUAUAUAUAUA	1122	20181	CUCGCUUAUAUAUAUAUA	1122	20199	UGAAUUAUAUAUAUAUAUA	2773
20199	AUACAGCAGUUAUAUAUAUA	1123	20199	AUACAGCAGUUAUAUAUAUA	1123	20217	CGAGCUUAUAUAUAUAUAUA	2774
20217	GAGGCUUAUAUAUAUAUAUA	1124	20217	GAGGCUUAUAUAUAUAUAUA	1124	20235	GUUCGAAAGGUAUAUAUAUA	2775
20235	CACUUGUUAUAUAUAUAUAUA	1125	20235	CACUUGUUAUAUAUAUAUAUA	1125	20253	AAUCCAUUAUAUAUAUAUAUA	2776
20253	UUCAGUUAUAUAUAUAUAUAUA	1126	20253	UUCAGUUAUAUAUAUAUAUAUA	1126	20271	CAAGUUGUUAUAUAUAUAUAUA	2777
20271	GGCGGCUUAUAUAUAUAUAUAUA	1127	20271	GGCGGCUUAUAUAUAUAUAUAUAUA	1127	20289	UCAUUAUAUAUAUAUAUAUAUA	2778
20289	AUAGGCUUAUAUAUAUAUAUAUAUA	1128	20289	AUAGGCUUAUAUAUAUAUAUAUAUAUA	1128	20307	AGCGCUUAUAUAUAUAUAUAUAUAUA	2779

(400/110\_US)

20307	UCACAAGAUUACCCACUUA	1129	20307	UCACAAGAUUACCCACUUA	1129	20325	UAGUGGUGAAUUCUUGUGA	2780
20325	AAAUUAGAGGAUUUAUCC	1130	20325	AAAUUAGAGGAUUUAUCC	1130	20343	GGAUAAAUCGUCUAAUUA	2781
20343	CCUUAUGGACACACAGUGA	1131	20343	CCUUAUGGACACACAGUGA	1131	20361	UCACUGUGCUGUCCAUAGG	2782
20361	AAAUAUACUACUAACAG	1132	20361	AAAUAUACUACUAACAG	1132	20379	CUGUUAUGAAGUAUUUUU	2783
20379	GAUGCGAAACAGGUUUAU	1133	20379	GAUGCGAAACAGGUUUAU	1133	20397	AUGAACCGUUGUGCGCAUC	2784
20397	UCAAAUGUGUGUUGUUGUG	1134	20397	UCAAAUGUGUGUUGUUGUG	1134	20415	CAGACACACACAUUUUGA	2785
20415	GUGAUUGAUUUUAUUAU	1135	20415	GUGAUUGAUUUUAUUAU	1135	20433	CAAGUAAAAGAUAAUACAC	2786
20433	GAUGACUUUGCGAGAUAA	1136	20433	GAUGACUUUGCGAGAUAA	1136	20451	UUAUCUCGACAAAGUCAUC	2787
20451	AUAAAGUCACAAAGAUUUG	1137	20451	AUAAAGUCACAAAGAUUUG	1137	20469	ACAAUUCUUGUGACUUAU	2788
20469	UCAGUGAUUUCAAAAGUGG	1138	20469	UCAGUGAUUUCAAAAGUGG	1138	20487	CCACUUUUGAAUACACUGA	2789
20487	GUCAAGGUUACAAUUGACU	1139	20487	GUCAAGGUUACAAUUGACU	1139	20505	AGUCAUUUGUAAACCUUGAC	2790
20505	UAUGCUAAAUAUUAUUA	1140	20505	UAUGCUAAAUAUUAUUA	1140	20523	UGAAUGAAUUAUCAGCAUA	2791
20523	AUGCUUUGUGUAAGGAUG	1141	20523	AUGCUUUGUGUAAGGAUG	1141	20541	CAUCCUUACACCAAGCAU	2792
20541	GGACAUUGUAAACCUUCU	1142	20541	GGACAUUGUAAACCUUCU	1142	20559	AGAAGGUUUAACAUGUCC	2793
20559	UACCCAAACUACAAGCAA	1143	20559	UACCCAAACUACAAGCAA	1143	20577	UUGCUUGUAGUUUUGGGUA	2794
20577	AGUGAGCGUGGCAACCCAG	1144	20577	AGUGAGCGUGGCAACCCAG	1144	20595	CUGGUUGCCACGCGUCGACU	2795
20595	GGUUGUGGAGGCUAACU	1145	20595	GGUUGUGGAGGCUAACU	1145	20613	AGUAGGCAUCGCAACACC	2796
20613	UUGUAAGAAGUGCAAGAA	1146	20613	UUGUAAGAAGUGCAAGAA	1146	20631	UUCUUUGCAUCUUGUACAA	2797
20631	AUGCUUUGGAAAGUGUG	1147	20631	AUGCUUUGGAAAGUGUG	1147	20649	CACACUUUUAAGAAAGCAU	2798
20649	GACCUUACAGAUUAUGGUG	1148	20649	GACCUUACAGAUUAUGGUG	1148	20667	CACCAUUAUUCUGAAGGUC	2799
20667	GAUUAUGCUUUAUUAUUA	1149	20667	GAUUAUGCUUUAUUAUUA	1149	20685	UUGGUAAACACAGCAUUUUC	2800
20685	AAAGAAUUAUGAUAUUAU	1150	20685	AAAGAAUUAUGAUAUUAU	1150	20703	CAUUAUUAUUAUUGCUUU	2801
20703	GUGGCAAGUAUUAUUAU	1151	20703	GUGGCAAGUAUUAUUAU	1151	20721	GUUGAGUAUUAUUAUUAU	2802
20721	CUGUGUAUUAUUAUUAU	1152	20721	CUGUGUAUUAUUAUUAU	1152	20739	UAUUAAAGUAUUAUUAUUA	2803
20739	ACAUUAUUAUUAUUAUUA	1153	20739	ACAUUAUUAUUAUUAUUA	1153	20757	GUACAGCUAAAGUAAGUGU	2804
20757	CCUUAUUAUUAUUAUUAU	1154	20757	CCUUAUUAUUAUUAUUAU	1154	20775	UAGCUCUUAUUAUUAUUAU	2805
20775	UUAUUAUUAUUAUUAUUA	1155	20775	UUAUUAUUAUUAUUAUUA	1155	20793	AGCAGACCAAAAGUGAAU	2806
20793	UCUGAAUUAUUAUUAUUA	1156	20793	UCUGAAUUAUUAUUAUUA	1156	20811	GUGCAACUCCUUUAUUAUUA	2807
20811	CCAGGUUAUUAUUAUUAU	1157	20811	CCAGGUUAUUAUUAUUAU	1157	20829	UGAGCAGACUUGUACCUUGG	2808
20829	AGCAAUUAUUAUUAUUAU	1158	20829	AGCAAUUAUUAUUAUUAU	1158	20847	CAGUUGGCAACCAUUAUUA	2809
20847	GGCACAUAUUAUUAUUAU	1159	20847	GGCACAUAUUAUUAUUAU	1159	20865	AUCCGAAAGUAGUGUGCC	2810
20865	UCAGAUUAUUAUUAUUAU	1160	20865	UCAGAUUAUUAUUAUUAU	1160	20883	CGAAGUUAUUAUUAUUAU	2811
20883	GUCUCCGAGCAUUAUUAU	1161	20883	GUCUCCGAGCAUUAUUAU	1161	20901	UAGAAUUAUUAUUAUUAU	2812
20901	ACUUUAUUAUUAUUAUUA	1162	20901	ACUUUAUUAUUAUUAUUA	1162	20919	CACAGUCCCAUUAUUAUUA	2813
20919	GCAACAGUAUUAUUAUUA	1163	20919	GCAACAGUAUUAUUAUUA	1163	20937	UAGCCGUUAUUAUUAUUA	2814
20937	AAUAAUUAUUAUUAUUAU	1164	20937	AAUAAUUAUUAUUAUUAU	1164	20955	UAUAAAGUCCCAUUAUUAU	2815
20955	AUUAAGUAUUAUUAUUAU	1165	20955	AUUAAGUAUUAUUAUUAU	1165	20973	GGUCAUUAUUAUUAUUAU	2816
20973	CCUAGGACCAAAUUAUUA	1166	20973	CCUAGGACCAAAUUAUUA	1166	20991	UCACAUUUUUGGUCCUAGG	2817
20991	ACAAAAGAAUUAUUAUUA	1167	20991	ACAAAAGAAUUAUUAUUA	1167	21009	UAGAGUUAUUAUUAUUAU	2818
21009	AAAGAGGAAUUAUUAUUA	1168	21009	AAAGAGGAAUUAUUAUUA	1168	21027	AAGUAAAACCCUUAUUAU	2819
21027	UAUCUGUGGAAUUAUUAU	1169	21027	UAUCUGUGGAAUUAUUAU	1169	21045	UUAUAAUUAUUAUUAUUA	2820
21045	AAGCAAAACUAGCCUUGG	1170	21045	AAGCAAAACUAGCCUUGG	1170	21063	CCAGGGCUAGUUUUUUGCUU	2821

(400/110\_US)

21063	GGUGGUUUAUAGCUGUAA	1171	21063	GGUGGUUUAUAGCUGUAA	1171	21081	UUAAGCUUAUAGAACACC	2822
21081	AAGUUAACAGAGCAUUCU	1172	21081	AAGUUAACAGAGCAUUCU	1172	21099	AAGUUAACAGAGCAUUCU	2823
21099	UGGAUUGGACCUUAUACA	1173	21099	UGGAUUGGACCUUAUACA	1173	21117	UGGAUUGGACCUUAUACA	2824
21117	AAGCUUAUUGGACCUUAU	1174	21117	AAGCUUAUUGGACCUUAU	1174	21135	AGAAUUGGACCUUAUACA	2825
21135	UAUGGUGGACCUUAUUG	1175	21135	UAUGGUGGACCUUAUUG	1175	21153	AGAAUUGGACCUUAUACA	2826
21153	GUUACAAUUGAAUUGCAU	1176	21153	GUUACAAUUGAAUUGCAU	1176	21171	AGAAUUGGACCUUAUACA	2827
21171	UUAUUAUUGGACCUUAU	1177	21171	UUAUUAUUGGACCUUAU	1177	21189	AGAAUUGGACCUUAUACA	2828
21189	UUAUUAUUGGACCUUAU	1178	21189	UUAUUAUUGGACCUUAU	1178	21207	AGAAUUGGACCUUAUACA	2829
21207	UUAUUAUUGGACCUUAU	1179	21207	UUAUUAUUGGACCUUAU	1179	21225	AGAAUUGGACCUUAUACA	2830
21225	UUAUUAUUGGACCUUAU	1180	21225	UUAUUAUUGGACCUUAU	1180	21243	AGAAUUGGACCUUAUACA	2831
21243	UUAUUAUUGGACCUUAU	1181	21243	UUAUUAUUGGACCUUAU	1181	21261	AGAAUUGGACCUUAUACA	2832
21261	UUAUUAUUGGACCUUAU	1182	21261	UUAUUAUUGGACCUUAU	1182	21279	AGAAUUGGACCUUAUACA	2833
21279	UUAUUAUUGGACCUUAU	1183	21279	UUAUUAUUGGACCUUAU	1183	21297	AGAAUUGGACCUUAUACA	2834
21297	UUAUUAUUGGACCUUAU	1184	21297	UUAUUAUUGGACCUUAU	1184	21315	AGAAUUGGACCUUAUACA	2835
21315	UUAUUAUUGGACCUUAU	1185	21315	UUAUUAUUGGACCUUAU	1185	21333	AGAAUUGGACCUUAUACA	2836
21333	UUAUUAUUGGACCUUAU	1186	21333	UUAUUAUUGGACCUUAU	1186	21351	AGAAUUGGACCUUAUACA	2837
21351	UUAUUAUUGGACCUUAU	1187	21351	UUAUUAUUGGACCUUAU	1187	21369	AGAAUUGGACCUUAUACA	2838
21369	UUAUUAUUGGACCUUAU	1188	21369	UUAUUAUUGGACCUUAU	1188	21387	AGAAUUGGACCUUAUACA	2839
21387	UUAUUAUUGGACCUUAU	1189	21387	UUAUUAUUGGACCUUAU	1189	21405	AGAAUUGGACCUUAUACA	2840
21405	UUAUUAUUGGACCUUAU	1190	21405	UUAUUAUUGGACCUUAU	1190	21423	AGAAUUGGACCUUAUACA	2841
21423	UUAUUAUUGGACCUUAU	1191	21423	UUAUUAUUGGACCUUAU	1191	21441	AGAAUUGGACCUUAUACA	2842
21441	UUAUUAUUGGACCUUAU	1192	21441	UUAUUAUUGGACCUUAU	1192	21459	AGAAUUGGACCUUAUACA	2843
21459	UUAUUAUUGGACCUUAU	1193	21459	UUAUUAUUGGACCUUAU	1193	21477	AGAAUUGGACCUUAUACA	2844
21477	UUAUUAUUGGACCUUAU	1194	21477	UUAUUAUUGGACCUUAU	1194	21495	AGAAUUGGACCUUAUACA	2845
21495	UUAUUAUUGGACCUUAU	1195	21495	UUAUUAUUGGACCUUAU	1195	21513	AGAAUUGGACCUUAUACA	2846
21513	UUAUUAUUGGACCUUAU	1196	21513	UUAUUAUUGGACCUUAU	1196	21531	AGAAUUGGACCUUAUACA	2847
21531	UUAUUAUUGGACCUUAU	1197	21531	UUAUUAUUGGACCUUAU	1197	21549	AGAAUUGGACCUUAUACA	2848
21549	UUAUUAUUGGACCUUAU	1198	21549	UUAUUAUUGGACCUUAU	1198	21567	AGAAUUGGACCUUAUACA	2849
21567	UUAUUAUUGGACCUUAU	1199	21567	UUAUUAUUGGACCUUAU	1199	21585	AGAAUUGGACCUUAUACA	2850
21585	UUAUUAUUGGACCUUAU	1200	21585	UUAUUAUUGGACCUUAU	1200	21603	AGAAUUGGACCUUAUACA	2851
21603	UUAUUAUUGGACCUUAU	1201	21603	UUAUUAUUGGACCUUAU	1201	21621	AGAAUUGGACCUUAUACA	2852
21621	UUAUUAUUGGACCUUAU	1202	21621	UUAUUAUUGGACCUUAU	1202	21639	AGAAUUGGACCUUAUACA	2853
21639	UUAUUAUUGGACCUUAU	1203	21639	UUAUUAUUGGACCUUAU	1203	21657	AGAAUUGGACCUUAUACA	2854
21657	UUAUUAUUGGACCUUAU	1204	21657	UUAUUAUUGGACCUUAU	1204	21675	AGAAUUGGACCUUAUACA	2855
21675	UUAUUAUUGGACCUUAU	1205	21675	UUAUUAUUGGACCUUAU	1205	21693	AGAAUUGGACCUUAUACA	2856
21693	UUAUUAUUGGACCUUAU	1206	21693	UUAUUAUUGGACCUUAU	1206	21711	AGAAUUGGACCUUAUACA	2857
21711	UUAUUAUUGGACCUUAU	1207	21711	UUAUUAUUGGACCUUAU	1207	21729	AGAAUUGGACCUUAUACA	2858
21729	UUAUUAUUGGACCUUAU	1208	21729	UUAUUAUUGGACCUUAU	1208	21747	AGAAUUGGACCUUAUACA	2859
21747	UUAUUAUUGGACCUUAU	1209	21747	UUAUUAUUGGACCUUAU	1209	21765	AGAAUUGGACCUUAUACA	2860
21765	UUAUUAUUGGACCUUAU	1210	21765	UUAUUAUUGGACCUUAU	1210	21783	AGAAUUGGACCUUAUACA	2861
21783	UUAUUAUUGGACCUUAU	1211	21783	UUAUUAUUGGACCUUAU	1211	21801	AGAAUUGGACCUUAUACA	2862
21801	UUAUUAUUGGACCUUAU	1212	21801	UUAUUAUUGGACCUUAU	1212	21819	AGAAUUGGACCUUAUACA	2863

(400/110\_US)

21819	AUUAUUAUUAACAAUUCUA	1213	21819	AUUAUUAUUAACAAUUCUA	1213	21837	UAGAAUUGUUAUUAUUAU	2864
21837	ACUAAUGUUGUUAUACGAG	1214	21837	ACUAAUGUUGUUAUACGAG	1214	21855	CUCGUUAACAACAUAUAGU	2865
21855	GCAUGUAACUUAUUAUUGU	1215	21855	GCAUGUAACUUAUUAUUGU	1215	21873	ACAUAUCAAAGUUAUACU	2866
21873	UGUGACAAACCCUUCUUG	1216	21873	UGUGACAAACCCUUCUUG	1216	21891	CAAGAAAGGGUUGUACACA	2867
21891	CGUGUUCUUAACCCUUG	1217	21891	CGUGUUCUUAACCCUUG	1217	21899	CCAUGGUUUAAGAAACAGC	2868
21899	GGUACACAGACAAUACUA	1218	21899	GGUACACAGACAAUACUA	1218	21927	UAGUAUGUCUGUGUAC	2869
21927	AUGAUUUCGAUUAUGCAU	1219	21927	AUGAUUUCGAUUAUGCAU	1219	21945	AUGCAUUAUCGAUUAUACU	2870
21945	UUUAUUGCACUUCGAGU	1220	21945	UUUAUUGCACUUCGAGU	1220	21963	ACUCGAAAGUGCAUUAUAA	2871
21963	UACUAUUCGAGUCCUUAU	1221	21963	UACUAUUCGAGUCCUUAU	1221	21981	AAAAGGCAUCAGAUUAUAA	2872
21981	UCGCUUGAGUUCGAGAA	1222	21981	UCGCUUGAGUUCGAGAA	1222	21999	UUUCGAAACAUCGAAACGA	2873
21999	AAGUCAGGUAAUUUAAC	1223	21999	AAGUCAGGUAAUUUAAC	1223	22017	GUUUAUUUAUCCUGACUU	2874
22017	CACUACGAGAGUUGUGU	1224	22017	CACUACGAGAGUUGUGU	1224	22035	ACACAAACUCUGUAAGUG	2875
22035	UUUAAAAUAAAGUGGU	1225	22035	UUUAAAAUAAAGUGGU	1225	22053	ACCAUCUUAUUUUUAAA	2876
22053	UUUCUUAUUAUUAAGG	1226	22053	UUUCUUAUUAUUAAGG	1226	22071	CCUUAUAAACAUAAGAAA	2877
22071	GGCUUAACAACUUAAGU	1227	22071	GGCUUAACAACUUAAGU	1227	22089	CAUCUAUAGGUUAAGCC	2878
22089	GUAGUUCGUAUUAACUU	1228	22089	GUAGUUCGUAUUAACUU	1228	22107	AAGGUAUACACGAACUAC	2879
22107	UCUGGUUUUAACUUAUGA	1229	22107	UCUGGUUUUAACUUAUGA	1229	22125	UCAAAGUGUUAUAAACCA	2880
22125	AAACCUUUUUUAAGUUGC	1230	22125	AAACCUUUUUUAAGUUGC	1230	22143	GCAUCUUAUAAUUAAGUUU	2881
22143	CCUCUUGGUUAUUAACUUA	1231	22143	CCUCUUGGUUAUUAACUUA	1231	22161	UAAUGUUAUUAUUAACAGG	2882
22161	ACAAUUUUUAAGGCCAUUC	1232	22161	ACAAUUUUUAAGGCCAUUC	1232	22179	GAUUGGCUUAUAAUUAUUGU	2883
22179	CUUACAGCCUUAUUAACUUG	1233	22179	CUUACAGCCUUAUUAACUUG	1233	22197	CAGGUGAAAGGCGUUAAG	2884
22197	GCUCAGACAUUAUUGGGCA	1234	22197	GCUCAGACAUUAUUGGGCA	1234	22215	UGCCGCAUUAUUAUUAAGC	2885
22215	ACGUCAGUAGCCUUAU	1235	22215	ACGUCAGUAGCCUUAU	1235	22233	AAUAGGCGUGCAGCUGACGU	2886
22233	UUUGUUGGCUUAUUAAGC	1236	22233	UUUGUUGGCUUAUUAAGC	1236	22251	GCUUUAUUAUUAUUAACAA	2887
22251	CCAACUUAUUAUUAAGC	1237	22251	CCAACUUAUUAUUAAGC	1237	22269	UGAGCAUUAUUAUUAAGUUG	2888
22269	AAGUAUGAUGAAUUAUGU	1238	22269	AAGUAUGAUGAAUUAUGU	1238	22287	UACCAUUUAUUAUUAUUAU	2889
22287	ACAAUACAGAUUGUUG	1239	22287	ACAAUACAGAUUGUUG	1239	22305	CAACAGCAUUGUUAUUAU	2890
22305	GAUUGUUCUUAUUAUUAU	1240	22305	GAUUGUUCUUAUUAUUAU	1240	22323	GUGGAUUUAUUAUUAUUAU	2891
22323	CUUGCUGAACUUAUUAU	1241	22323	CUUGCUGAACUUAUUAU	1241	22341	AGCAUUUAUUAUUAUUAU	2892
22341	UCUGUUAAGAGCUUAUUA	1242	22341	UCUGUUAAGAGCUUAUUA	1242	22359	UCUCAAGCUCUUAUUAU	2893
22359	AUUGACAAAGGAUUAUUA	1243	22359	AUUGACAAAGGAUUAUUA	1243	22377	GGUAAUUAUUAUUAUUAU	2894
22377	CAGACCUUAUUAUUAUUA	1244	22377	CAGACCUUAUUAUUAUUA	1244	22395	CCUGAAUUAUUAUUAUUAU	2895
22395	GUUGUUCUUAUUAUUAU	1245	22395	GUUGUUCUUAUUAUUAU	1245	22413	CAUCUCUGAGGGAUUAU	2896
22413	GUUGAGAUUAUUAUUAU	1246	22413	GUUGAGAUUAUUAUUAU	1246	22431	UAUUAUUAUUAUUAUUAU	2897
22431	AUUAUUAUUAUUAUUAU	1247	22431	AUUAUUAUUAUUAUUAU	1247	22449	AAGGACAAAGUUAUUAU	2898
22449	UUUGAGAGGUUAUUAUUA	1248	22449	UUUGAGAGGUUAUUAUUA	1248	22467	CAUUAUUAUUAUUAUUAU	2899
22467	GUUUAUUAUUAUUAUUAU	1249	22467	GUUUAUUAUUAUUAUUAU	1249	22485	CAGAAGGGAUUAUUAUUAU	2900
22485	GUCUUAUUAUUAUUAUUA	1250	22485	GUCUUAUUAUUAUUAUUA	1250	22503	UUCUCUUAUUAUUAUUAU	2901
22503	AAAAAUUAUUAUUAUUAU	1251	22503	AAAAAUUAUUAUUAUUAU	1251	22521	CACAUAUUAUUAUUAUUAU	2902
22521	GUUGCUGAUUAUUAUUAU	1252	22521	GUUGCUGAUUAUUAUUAU	1252	22539	GCACAGUUAUUAUUAUUAU	2903
22539	CUCUACACUUAUUAUUAU	1253	22539	CUCUACACUUAUUAUUAU	1253	22557	AAAAUUAUUAUUAUUAUUAU	2904
22557	UUUUAUUAUUAUUAUUAU	1254	22557	UUUUAUUAUUAUUAUUAU	1254	22575	AGCACUUAUUAUUAUUAUUAU	2905

(400/110\_US)

22575	UAUGGCGUUUCUGCCACUA	1255	22575	UAUGGCGUUUCUGCCACUA	1255	22593	UAGUGGCAGAAACGCCAUA	2906
22593	AAGUUGAAUGAUUUCU	1256	22593	AAGUUGAAUGAUUUCU	1256	22611	AGCAAGAUCAUUCAAU	2907
22611	UUCUCCAAUGUCUAGCAG	1257	22611	UUCUCCAAUGUCUAGCAG	1257	22629	CUGCAUAGCAUUGGAGAA	2908
22629	GAUUCUUUUGUAGUCAA	1258	22629	GAUUCUUUUGUAGUCAA	1258	22647	CCUUGACUACAAAGAAUC	2909
22647	GGAGAUUGUAGUAGACAA	1259	22647	GGAGAUUGUAGUAGACAA	1259	22665	UUUGUCUUAUUAUUAU	2910
22665	UAUGGCGCCAGGACAAACUG	1260	22665	UAUGGCGCCAGGACAAACUG	1260	22683	CAGUUGUCUUGGCGCUAU	2911
22683	GGUUGUUAUUGGUAUUA	1261	22683	GGUUGUUAUUGGUAUUA	1261	22701	UAUAUAGCAUUAUUAU	2912
22701	AAUAUAUUAUUGGAGAU	1262	22701	AAUAUAUUAUUGGAGAU	1262	22719	CAUCUGGCAUUAUUAU	2913
22719	GAUUAUUGGUGUUGUC	1263	22719	GAUUAUUGGUGUUGUC	1263	22737	GGACAACCAUUAUUAU	2914
22737	CUUGCUUGGAAUUAUUA	1264	22737	CUUGCUUGGAAUUAUUA	1264	22755	UCCUAGAUUUAUUAUUA	2915
22755	AACAUAUUAUUAUUAU	1265	22755	AACAUAUUAUUAUUAU	1265	22773	UUGAAGUAGCAUUAUUA	2916
22773	ACUGGUUAUUAUUAUUA	1266	22773	ACUGGUUAUUAUUAUUA	1266	22791	UAUAUAUUAUUAUUAU	2917
22791	AAUAUAUUAUUAUUAU	1267	22791	AAUAUAUUAUUAUUAU	1267	22809	GUCUAAGAUUAUUAUUA	2918
22809	CAUGGCAAGCUUAGGCCU	1268	22809	CAUGGCAAGCUUAGGCCU	1268	22827	AGGCCUUAAGCUUAGGCCU	2919
22827	UUUGAGAGAGACAUUAU	1269	22827	UUUGAGAGAGACAUUAU	1269	22845	UAGAUUUGUCUCUCUCAA	2920
22845	AAUGUGCCUUCUGCCUG	1270	22845	AAUGUGCCUUCUGCCUG	1270	22863	CAGGGAGAAAGGCCACAU	2921
22863	GAUGGCAACCUUGCACCC	1271	22863	GAUGGCAACCUUGCACCC	1271	22881	GGUGGCAAGGUUUGCCAU	2922
22881	CCACCGUUCUUAUUAU	1272	22881	CCACCGUUCUUAUUAU	1272	22899	AACAUAUUAAGAGAGGUG	2923
22899	UAUUGGCAUUAUUAUUA	1273	22899	UAUUGGCAUUAUUAUUA	1273	22917	AAUUAUUAUUGGCCAUA	2924
22917	UAUGGUUAUUAUUAUUA	1274	22917	UAUGGUUAUUAUUAUUA	1274	22935	UAGUGGUUAUUAUUAUUA	2925
22935	ACUGGCAUUGGCUUACCA	1275	22935	ACUGGCAUUGGCUUACCA	1275	22953	GUUGGUAGCCAUUAUUA	2926
22953	CCUUAUUAUUAUUAUUA	1276	22953	CCUUAUUAUUAUUAUUA	1276	22971	GUACUACCAUUAUUAUUA	2927
22971	CUUUCUUUUAUUAUUAU	1277	22971	CUUUCUUUUAUUAUUAU	1277	22989	UUAUAUUAUUAUUAUUA	2928
22989	AAUGGCAUUAUUAUUAU	1278	22989	AAUGGCAUUAUUAUUAU	1278	23007	AAACCGUGGCGGUGCAU	2929
23007	UGUGGCAUUAUUAUUAU	1279	23007	UGUGGCAUUAUUAUUAU	1279	23025	UGGAUUAUUAUUGGCCA	2930
23025	ACUGGCAUUAUUAUUAU	1280	23025	ACUGGCAUUAUUAUUAU	1280	23043	GGUUCUUAUUAUUGGCCA	2931
23043	CAGUGGCAUUAUUAUUA	1281	23043	CAGUGGCAUUAUUAUUA	1281	23061	AAUUAUAUUAUUAUUAU	2932
23061	UUUAUUGGACUUAUUAU	1282	23061	UUUAUUGGACUUAUUAU	1282	23079	UACCAUUAUUAUUAUUA	2933
23079	ACUGGUGUUAUUAUUAU	1283	23079	ACUGGUGUUAUUAUUAU	1283	23097	AAGGAUUAUUAUUAUUA	2934
23097	UCUUAUUAUUAUUAUUA	1284	23097	UCUUAUUAUUAUUAUUA	1284	23115	GUUGAAUUAUUAUUAUUA	2935
23115	CCAUUAUUAUUAUUAUUA	1285	23115	CCAUUAUUAUUAUUAUUA	1285	23133	GGCCAAUUAUUAUUAUUA	2936
23133	CGUGAUUAUUAUUAUUA	1286	23133	CGUGAUUAUUAUUAUUA	1286	23151	UGAAUUAUUAUUAUUAU	2937
23151	ACUGAUUAUUAUUAUUA	1287	23151	ACUGAUUAUUAUUAUUA	1287	23169	GAUCUUAUUAUUAUUAU	2938
23169	CCUUAUUAUUAUUAUUA	1288	23169	CCUUAUUAUUAUUAUUA	1288	23187	AUUAUUAUUAUUAUUAU	2939
23187	UAAGAUUAUUAUUAUUA	1289	23187	UAAGAUUAUUAUUAUUA	1289	23205	CGCAAGUUAUUAUUAUUA	2940
23205	GCUUAUUAUUAUUAUUA	1290	23205	GCUUAUUAUUAUUAUUA	1290	23223	CACUUAUUAUUAUUAUUA	2941
23223	GUUAUUAUUAUUAUUAU	1291	23223	GUUAUUAUUAUUAUUAU	1291	23241	UUGUUAUUAUUAUUAUUA	2942
23241	AAUGUUAUUAUUAUUAU	1292	23241	AAUGUUAUUAUUAUUAU	1292	23259	CAUUAUUAUUAUUAUUA	2943
23259	GCUGUUAUUAUUAUUAU	1293	23259	GCUGUUAUUAUUAUUAU	1293	23277	CAUUAUUAUUAUUAUUA	2944
23277	GUUAUUAUUAUUAUUAU	1294	23277	GUUAUUAUUAUUAUUAU	1294	23295	AAUUAUUAUUAUUAUUA	2945
23295	UCUUAUUAUUAUUAUUA	1295	23295	UCUUAUUAUUAUUAUUA	1295	23313	CUGCAUUAUUAUUAUUA	2946
23313	GAUCAUUAUUAUUAUUA	1296	23313	GAUCAUUAUUAUUAUUA	1296	23331	AAGCUGGUGUUAUUAUUA	2947



(400/110\_US)

23331	UGGCGCAUAUAUUCUACUG	1297	23331	UGGCGCAUAUAUUCUACUG	1297	23349	CAGUAGAAUAUAUGCGCCA	2948
23349	GGAAACAUAUUAUCCAGA	1298	23349	GGAAACAUAUUAUCCAGA	1298	23367	UCUGAAUAUAUUGUUUCC	2949
23367	ACUACAAGCAGGUGUCUUA	1299	23367	ACUACAAGCAGGUGUCUUA	1299	23385	UAGGACGCCUGCUUGAGU	2950
23385	AUAGGAGCUGGACUUGCG	1300	23385	AUAGGAGCUGGACUUGCG	1300	23403	CGACUGCUCAGCUCUUAU	2951
23403	GACACUUCUUAUGAGUGCG	1301	23403	GACACUUCUUAUGAGUGCG	1301	23421	CGCACUCAUAAGAAUGUC	2952
23421	GACAUUCCUAUUGGAGCUG	1302	23421	GACAUUCCUAUUGGAGCUG	1302	23439	CAGCUCCAUAAGGAUUGC	2953
23439	GGCAUUGUGCUAGUUAAC	1303	23439	GGCAUUGUGCUAGUUAAC	1303	23457	GGUAUAAGCACAAUUGCC	2954
23457	CAUACAGUUCUUAUUAAC	1304	23457	CAUACAGUUCUUAUUAAC	1304	23475	GUAAUAAGAAACUGUAUG	2955
23475	CGUAUAGUAGCCAAUAU	1305	23475	CGUAUAGUAGCCAAUAU	1305	23493	AUUUUUGCUAGUACUACG	2956
23493	UCUAUUGUGGCUUAUACUA	1306	23493	UCUAUUGUGGCUUAUACUA	1306	23511	UAGUAUAAGCCACAAUAGA	2957
23511	AUGUCUUAAGGUGUGUAUA	1307	23511	AUGUCUUAAGGUGUGUAUA	1307	23529	UAGCAGCACCUAAGACAU	2958
23529	AGUUCAAUUGCUUACUCUA	1308	23529	AGUUCAAUUGCUUACUCUA	1308	23547	UAGAGUAAGCAUAUUAU	2959
23547	AAUACACCAUUGCUUAUAC	1309	23547	AAUACACCAUUGCUUAUAC	1309	23565	GUUAGCAUUGGUGUUAU	2960
23565	CCUACUAAACUUAUUAUA	1310	23565	CCUACUAAACUUAUUAUA	1310	23583	UAAUUGAAAGUUAUAGG	2961
23583	AGCAUUAACACAGAAUA	1311	23583	AGCAUUAACACAGAAUA	1311	23601	UUAUUCUGUAGUAUUGCU	2962
23601	AUGCCUGUUAUUGGCUA	1312	23601	AUGCCUGUUAUUGGCUA	1312	23619	UAGCAUAAGAAACAGGCU	2963
23619	AAACCCUCCGUAUUGUA	1313	23619	AAACCCUCCGUAUUGUA	1313	23637	UAGCAUUAAGGAGGUUAU	2964
23637	AAUAGUACUUCUGCGGAG	1314	23637	AAUAGUACUUCUGCGGAG	1314	23655	CUCGAGAGUAGCAUAU	2965
23655	GAUUGUACUUAUUGGCUA	1315	23655	GAUUGUACUUAUUGGCUA	1315	23673	UAGCAUUAAGGAGGUUAU	2966
23673	AAUUGCUUCCUUAUUAUG	1316	23673	AAUUGCUUCCUUAUUAUG	1316	23691	CAUAUUGGAGAGCAAAU	2967
23691	GUUAGCUUUGCACACAAC	1317	23691	GUUAGCUUUGCACACAAC	1317	23709	GUUGUGCAAAAGCUUACC	2968
23709	CUAAUUGGUGCUCUACAG	1318	23709	CUAAUUGGUGCUCUACAG	1318	23727	CUAGAGUGCAGCAUUAUAG	2969
23727	GGUUAUUGGUGCAGACAG	1319	23727	GGUUAUUGGUGCAGACAG	1319	23745	CCUUGUAGCAGCAUUAUACC	2970
23745	GAUCGCAACACGUGAAG	1320	23745	GAUCGCAACACGUGAAG	1320	23763	CUUACGUGUGUUGCGAUC	2971
23763	GUGUUGCGUCAAAGUCAAAC	1321	23763	GUGUUGCGUCAAAGUCAAAC	1321	23781	GUUAGACUUGAGCGCAAC	2972
23781	CAAAUGUACAAAAGCCCAA	1322	23781	CAAAUGUACAAAAGCCCAA	1322	23799	UUGGGUUAUUGUACAUUUG	2973
23799	ACUUUGAAUUAUUGGUG	1323	23799	ACUUUGAAUUAUUGGUG	1323	23817	CACCAAAUUAUUAUUAU	2974
23817	GGUUUAUUAUUAUUAUUA	1324	23817	GGUUUAUUAUUAUUAUUA	1324	23835	UUUGUAAAUUAUUAUUAU	2975
23835	AUAUUAUUAUUAUUAUUA	1325	23835	AUAUUAUUAUUAUUAUUA	1325	23853	UUAAGAGGUGUAGUUAUUA	2976
23853	AAGCCAAUUAUUAUUAUUA	1326	23853	AAGCCAAUUAUUAUUAUUA	1326	23871	AAGCCUUAUUAUUAUUAU	2977
23871	UUUAUUAUUAUUAUUAUUA	1327	23871	UUUAUUAUUAUUAUUAUUA	1327	23889	AGAGCAAGUCCUUAUUAU	2978
23889	UUUAUUAUUAUUAUUAUUA	1328	23889	UUUAUUAUUAUUAUUAUUA	1328	23907	CGAGUGUCCUUAUUAUUA	2979
23907	GCUGUUGGUGUUAUUAUUA	1329	23907	GCUGUUGGUGUUAUUAUUA	1329	23925	UCAUGAAGCAGCAUUAUUA	2980
23925	AAGCAUUAUUAUUAUUAUUA	1330	23925	AAGCAUUAUUAUUAUUAUUA	1330	23943	GGCAUUGGCAUUAUUAUUA	2981
23943	CUAGGUGUAUUAUUAUUAUUA	1331	23943	CUAGGUGUAUUAUUAUUAUUA	1331	23961	UAGCAUUAUUAUUAUUAUUA	2982
23961	AGAGUUAUUAUUAUUAUUAUUA	1332	23961	AGAGUUAUUAUUAUUAUUAUUA	1332	23979	CGCAUUAUUAUUAUUAUUA	2983
23979	CAGAAGUUAUUAUUAUUAUUA	1333	23979	CAGAAGUUAUUAUUAUUAUUA	1333	23997	UAGUUAUUAUUAUUAUUAUUA	2984
23997	ACAGUUGGUGGUGGUGGUGGUG	1334	23997	ACAGUUGGUGGUGGUGGUGGUG	1334	24015	GCAGAGGUGGCAUUAUUAUUA	2985
24015	CUCACUGAUAUUAUUAUUAUUA	1335	24015	CUCACUGAUAUUAUUAUUAUUA	1335	24033	CAUUAUUAUUAUUAUUAUUA	2986
24033	CGUGGUGGUGGUGGUGGUGGUG	1336	24033	CGUGGUGGUGGUGGUGGUGGUG	1336	24051	GAGCAGUUAUUAUUAUUAUUA	2987
24051	CUAGUUAUUAUUAUUAUUAUUA	1337	24051	CUAGUUAUUAUUAUUAUUAUUA	1337	24069	UGGCAUUAUUAUUAUUAUUA	2988
24069	ACUGGUGGUGGUGGUGGUGGUG	1338	24069	ACUGGUGGUGGUGGUGGUGGUG	1338	24087	CAUUAUUAUUAUUAUUAUUA	2989

(400/110\_US)

24087	GGUGCUGGCGCUCUUC	1339	24087	GGUGCUGGCGCUCUUC	1339	24105	GAAGAGCAGCGCAGCACC	2990
24105	CAAAUACCUUUGCUAUGC	1340	24105	CAAAUACCUUUGCUAUGC	1340	24123	GCAUAGCAAAAGGUUUG	2991
24123	CAAAUGGCAUAGGUUA	1341	24123	CAAAUGGCAUAGGUUA	1341	24141	UGAACCUUUAUGCCAUUG	2992
24141	AAUGGCAUUGAGUUAACC	1342	24141	AAUGGCAUUGAGUUAACC	1342	24159	GGUUAACUCCAAUGCCAUU	2993
24159	CAAAUGUUCUUAUGAGA	1343	24159	CAAAUGUUCUUAUGAGA	1343	24177	UCUAUAGAGAACAUUUG	2994
24177	AACCAAAACAAUCCCA	1344	24177	AACCAAAACAAUCCCA	1344	24195	UGGCGAUUUGUUUUGGUU	2995
24195	AACCAAAACAAUCCCA	1345	24195	AACCAAAACAAUCCCA	1345	24213	UCGCCUUGUAAAUUGGUU	2996
24213	AUUAUUAUUAUUAUUA	1346	24213	AUUAUUAUUAUUAUUA	1346	24231	AUUCUUGAUUUGACUAAU	2997
24231	UCACUUAACAAUUAUUA	1347	24231	UCACUUAACAAUUAUUA	1347	24249	UUGAGUUGUUGUUAAGUA	2998
24249	ACUGCAUUGGCAAGCUG	1348	24249	ACUGCAUUGGCAAGCUG	1348	24267	GCAGUUGUUGUUAAGUA	2999
24267	CAAGAGGUUUAUUAUUA	1349	24267	CAAGAGGUUUAUUAUUA	1349	24285	UGUGGUUAACAAAGCUCU	3000
24285	AAUGCUAAGCAUUAACA	1350	24285	AAUGCUAAGCAUUAACA	1350	24303	UGUUUAUGCUUGAGCAU	3001
24303	ACACUUAUUAUUAUUA	1351	24303	ACACUUAUUAUUAUUA	1351	24321	UUAUGUUGUUAUUAAGUGU	3002
24321	AGCUCUUAUUAUUAUUA	1352	24321	AGCUCUUAUUAUUAUUA	1352	24339	UUGACCCAAAUUAAGAGCU	3003
24339	AUUAUUAUUAUUAUUA	1353	24339	AUUAUUAUUAUUAUUA	1353	24357	CAUUAUAGCACACUUAUUA	3004
24357	GAUUAUUAUUAUUAUUA	1354	24357	GAUUAUUAUUAUUAUUA	1354	24375	CAAGUCGCGAAAGGAUUA	3005
24375	GAUUAUUAUUAUUAUUA	1355	24375	GAUUAUUAUUAUUAUUA	1355	24393	CCUGCGCUCGACUUAUUA	3006
24393	GUACAAUUAUUAUUAUUA	1356	24393	GUACAAUUAUUAUUAUUA	1356	24411	UUAACCUUGUUAUUAUUA	3007
24411	AUUAUUAUUAUUAUUA	1357	24411	AUUAUUAUUAUUAUUA	1357	24429	UUAAGUUGUUAUUAUUA	3008
24429	AGGUUAUUAUUAUUAUUA	1358	24429	AGGUUAUUAUUAUUAUUA	1358	24447	UUAAGUUGUUAUUAUUA	3009
24447	AGGUUAUUAUUAUUAUUA	1359	24447	AGGUUAUUAUUAUUAUUA	1359	24465	CCUGUUAUUAUUAUUAUUA	3010
24465	CGUGUUAUUAUUAUUAUUA	1360	24465	CGUGUUAUUAUUAUUAUUA	1360	24483	AAAGCUGUUAUUAUUAUUA	3011
24483	UCUGUUAUUAUUAUUAUUA	1361	24483	UCUGUUAUUAUUAUUAUUA	1361	24501	UAGCAUUAUUAUUAUUAUUA	3012
24501	ACUUAUUAUUAUUAUUAUUA	1362	24501	ACUUAUUAUUAUUAUUAUUA	1362	24519	CACACUUAUUAUUAUUAUUA	3013
24519	GUUUAUUAUUAUUAUUAUUA	1363	24519	GUUUAUUAUUAUUAUUAUUA	1363	24537	UUUUAUUAUUAUUAUUAUUA	3014
24537	AGGUUAUUAUUAUUAUUAUUA	1364	24537	AGGUUAUUAUUAUUAUUAUUA	1364	24555	UUAACCAUUAUUAUUAUUAUUA	3015
24555	AGGUUAUUAUUAUUAUUAUUA	1365	24555	AGGUUAUUAUUAUUAUUAUUA	1365	24573	ACUUAUUAUUAUUAUUAUUA	3016
24573	UUAUUAUUAUUAUUAUUAUUA	1366	24573	UUAUUAUUAUUAUUAUUAUUA	1366	24591	GGGUGUUAUUAUUAUUAUUA	3017
24591	CCGUAUUAUUAUUAUUAUUAUUA	1367	24591	CCGUAUUAUUAUUAUUAUUAUUA	1367	24609	GGGUAUUAUUAUUAUUAUUA	3018
24609	CUUAUUAUUAUUAUUAUUAUUA	1368	24609	CUUAUUAUUAUUAUUAUUAUUA	1368	24627	GCACUUAUUAUUAUUAUUAUUA	3019
24627	CUUAUUAUUAUUAUUAUUAUUA	1369	24627	CUUAUUAUUAUUAUUAUUAUUA	1369	24645	AGUUAUUAUUAUUAUUAUUAUUA	3020
24645	UUAUUAUUAUUAUUAUUAUUAUUA	1370	24645	UUAUUAUUAUUAUUAUUAUUAUUA	1370	24663	UUAUUAUUAUUAUUAUUAUUAUUA	3021
24663	UUAUUAUUAUUAUUAUUAUUAUUA	1371	24663	UUAUUAUUAUUAUUAUUAUUAUUA	1371	24681	CUUUAUUAUUAUUAUUAUUAUUAUUA	3022
24681	CUUUAUUAUUAUUAUUAUUAUUAUUA	1372	24681	CUUUAUUAUUAUUAUUAUUAUUAUUA	1372	24699	CUUUAUUAUUAUUAUUAUUAUUAUUA	3023
24699	CUUUAUUAUUAUUAUUAUUAUUAUUA	1373	24699	CUUUAUUAUUAUUAUUAUUAUUAUUA	1373	24717	CUUUAUUAUUAUUAUUAUUAUUAUUA	3024
24717	CUUUAUUAUUAUUAUUAUUAUUAUUA	1374	24717	CUUUAUUAUUAUUAUUAUUAUUAUUA	1374	24735	UUAUUAUUAUUAUUAUUAUUAUUA	3025
24735	UUAUUAUUAUUAUUAUUAUUAUUAUUA	1375	24735	UUAUUAUUAUUAUUAUUAUUAUUAUUA	1375	24753	AAUUAUUAUUAUUAUUAUUAUUAUUA	3026
24753	AAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1376	24753	AAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1376	24771	UUAUUAUUAUUAUUAUUAUUAUUAUUA	3027
24771	UUAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1377	24771	UUAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1377	24789	AGUUAUUAUUAUUAUUAUUAUUAUUAUUA	3028
24789	AGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1378	24789	AGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1378	24807	CGUUAUUAUUAUUAUUAUUAUUAUUAUUA	3029
24807	CGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1379	24807	CGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1379	24825	UGUUAUUAUUAUUAUUAUUAUUAUUAUUA	3030
24825	UGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1380	24825	UGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUA	1380	24843	GAGUUAUUAUUAUUAUUAUUAUUAUUAUUA	3031

(400/110\_US)

24843	CUGCAACCGUAGCUUAGCU	1381	24843	CUGCAACCGUAGCUUAGCU	1381	24861	AGUCAAGCUCAGGUUGCAG	3032
24861	UCAUUCAAAGAGAGCUGG	1382	24861	UCAUUCAAAGAGAGCUGG	1382	24879	CCAGCUCUUCUUUGAAUGA	3033
24879	GACAAGUACUCAAACU	1383	24879	GACAAGUACUCAAACU	1383	24897	GAUUUUUGAAGUACUUGUC	3034
24897	CAUACUACCCAGAUUG	1384	24897	CAUACUACCCAGAUUG	1384	24915	CAACUUCUGGUAGUUG	3035
24915	GAUUCUGGCAUUCAG	1385	24915	GAUUCUGGCAUUCAG	1385	24933	CUGAAUUGCCCAAGUCC	3036
24933	GGCAUUAACGCUUCUGC	1386	24933	GGCAUUAACGCUUCUGC	1386	24951	CGACAGAAGCGUUAUUGCC	3037
24951	GUCAACUUCAAAAGAAA	1387	24951	GUCAACUUCAAAAGAAA	1387	24969	UUUCUUUUUGAAUUGGAC	3038
24969	AUUGCCGCUCAUAGAGG	1388	24969	AUUGCCGCUCAUAGAGG	1388	24987	CCUCAUUGAGGCGGCUCAU	3039
24987	GUCGUAAAAUUUAAUG	1389	24987	GUCGUAAAAUUUAAUG	1389	25005	CAUUUAAUUUUUAGCGAC	3040
25005	GAUACUACUAGCUCU	1390	25005	GAUACUACUAGCUCU	1390	25023	GAGUCAAUGAGUAGUUC	3041
25023	CAAGAAUUGGAAAAUUG	1391	25023	CAAGAAUUGGAAAAUUG	1391	25041	GAUUUUUCCCAUUCUUG	3042
25041	GAGCAUUAUUAUUGC	1392	25041	GAGCAUUAUUAUUGC	1392	25059	GCCAUUUAUUAUUGCUC	3043
25059	CCUUGGUUUGUUGGCU	1393	25059	CCUUGGUUUGUUGGCU	1393	25077	CGAGCAAACAUACCAAGG	3044
25077	GGCUUUAUUGGCUAA	1394	25077	GGCUUUAUUGGCUAA	1394	25095	UUAUCCAGCAUAGAGCC	3045
25095	AUUGCCAUUGGCUUUA	1395	25095	AUUGCCAUUGGCUUUA	1395	25113	UACCAUAGCAGGSCAAU	3046
25113	ACAUCUUGCUUUGGUA	1396	25113	ACAUCUUGCUUUGGUA	1396	25131	UGCAACAAAGCAAGAUUGU	3047
25131	AUGACUAGUUGGCUU	1397	25131	AUGACUAGUUGGCUU	1397	25149	AACUGCAACCAUAGUACU	3048
25149	UGCCUCAAGGUGGCU	1398	25149	UGCCUCAAGGUGGCU	1398	25167	AGCAUGCACCCUUGAGGCA	3049
25167	UCUUGGUUUCUUGGCA	1399	25167	UCUUGGUUUCUUGGCA	1399	25185	UGCAGAAAGCAACCAAGA	3050
25185	AAGUUGAGGAGGAGU	1400	25185	AAGUUGAGGAGGAGU	1400	25203	AGUCAUCCUACAACAUU	3051
25203	UCUGAGCAGUUCUAGG	1401	25203	UCUGAGCAGUUCUAGG	1401	25221	CCUUGAAACUGGCUACAG	3052
25221	GGUGCAAAUUAUUA	1402	25221	GGUGCAAAUUAUUA	1402	25239	UGUAUUAUUAUUGACAC	3053
25239	ACAAACGAAUUAUGGA	1403	25239	ACAAACGAAUUAUGGA	1403	25257	UCCAAAGUUCGUUUUGU	3054
25257	AUUUGUUUAGAGAUUUU	1404	25257	AUUUGUUUAGAGAUUUU	1404	25275	AAAAUCUCAAACAAU	3055
25275	UAUCUUGGAGUAAUUA	1405	25275	UAUCUUGGAGUAAUUA	1405	25293	GUAAUUAUCCAGAGUAA	3056
25293	CUGCACAGCCAGUAAAU	1406	25293	CUGCACAGCCAGUAAAU	1406	25311	AUUUUAUUGGCUUGCAG	3057
25311	UUGACAAUGCUUGCUC	1407	25311	UUGACAAUGCUUGCUC	1407	25329	GCAGGAGAGCAUUGUCA	3058
25329	CAAGUACUUGUACUAC	1408	25329	CAAGUACUUGUACUAC	1408	25347	GUAGCAUAGCAUAGUUG	3059
25347	CAGCAACGUAUCCGCU	1409	25347	CAGCAACGUAUCCGCU	1409	25365	UGUAGCGGUUUGGCUUG	3060
25365	AAGCCUACUCCUUCGG	1410	25365	AAGCCUACUCCUUCGG	1410	25383	CCGAAAGGAGUGAGGCUU	3061
25383	GAUGGCUUGUUAUUGGCU	1411	25383	GAUGGCUUGUUAUUGGCU	1411	25401	ACGCCAAUACCAAGCAU	3062
25401	UUGCAUUCUUGGCUUUU	1412	25401	UUGCAUUCUUGGCUUUU	1412	25419	AAAACAGCAAGAAUUGCAA	3063
25419	UUCAGAGCGUACCAAAU	1413	25419	UUCAGAGCGUACCAAAU	1413	25437	AUUUUGGAGCGCUGAA	3064
25437	UAUUUGCGUCAAUAAAG	1414	25437	UAUUUGCGUCAAUAAAG	1414	25455	CUUUUAUUGAGCGCAUUA	3065
25455	GAUGGCGUACCCUUA	1415	25455	GAUGGCGUACCCUUA	1415	25473	UAAAGGCUAGCUGCUGAA	3066
25473	AUAAGGCUUCCAGUUAU	1416	25473	AUAAGGCUUCCAGUUAU	1416	25491	AUGAAGUAGGAGCCUUAU	3067
25491	UUUGCAUUAUUGGCU	1417	25491	UUUGCAUUAUUGGCU	1417	25509	AGCAGCAUAAUUGCAAA	3068
25509	UAUUUGUUAUUAUUAU	1418	25509	UAUUUGUUAUUAUUAU	1418	25527	GAUAGAGUUAACAAUUA	3069
25527	CACAUUUUGGCUUGC	1419	25527	CACAUUUUGGCUUGC	1419	25545	GCGAAGCAAAAGAUUG	3070
25545	CUGCAGGUAGGAGCGCA	1420	25545	CUGCAGGUAGGAGCGCA	1420	25563	UGCGCUUCCUACCGCAG	3071
25563	AAUUUUUGUACCUUAGC	1421	25563	AAUUUUUGUACCUUAGC	1421	25581	GCAUAGAGGUACAAAUU	3072
25581	CCUUGAUUAUUAUUAU	1422	25581	CCUUGAUUAUUAUUAU	1422	25599	UGUAGAAAUUAUUAUUAU	3073



(400/110\_US)

25599	AAUGCAUACACGCAUGAG	1423	25599	AAUGCAUACACGCAUGAG	1423	25617	CUAUGCGGUUGAUGCAUU	3074
25617	GAUUUAUUAUGAGUUG	1424	25617	GAUUUAUUAUGAGUUG	1424	25635	CAACAUUCUAUUAUUC	3075
25635	GGCUUUGUUGAAGUGCAA	1425	25635	GGCUUUGUUGAAGUGCAA	1425	25653	UUGCACUUCACAAAGGCC	3076
25653	AAUCCAAGAACCCAUUACU	1426	25653	AAUCCAAGAACCCAUUACU	1426	25671	AGUAUUGGUUUCUUGGAUU	3077
25671	UUUAUGAUGCCAAUACUU	1427	25671	UUUAUGAUGCCAAUACUU	1427	25689	AAGUAGUUGGCAUCAUAAA	3078
25689	UUGUUUGUGGCAUACACA	1428	25689	UUGUUUGUGGCAUACACA	1428	25707	UGUGUGGCGCCAAUAAU	3079
25707	AUAUAUAGACUACUGUUAU	1429	25707	AUAUAUAGACUACUGUUAU	1429	25725	AUAUAGUAGUAGUUAU	3080
25725	UACCAUAUACAGUGUCAC	1430	25725	UACCAUAUACAGUGUCAC	1430	25743	GUGACACUGUUAUUGGUA	3081
25743	CAGUAUAAUUGUCUUAU	1431	25743	CAGUAUAAUUGUCUUAU	1431	25761	GUACGACAAUUGUACUG	3082
25761	CUGAAGGUGACGCAUUC	1432	25761	CUGAAGGUGACGCAUUC	1432	25779	GAUUGCGGUCACCUUACG	3083
25779	CAACACCAAAACUCAAAGA	1433	25779	CAACACCAAAACUCAAAGA	1433	25797	UCUUUGAGUUUUGGUGUUG	3084
25797	AAGAUUACCAAAUUGUGG	1434	25797	AAGAUUACCAAAUUGUGG	1434	25815	CCACAAUUUUGUAGUCUU	3085
25815	GUUAUUGUGAGGUAAGGCA	1435	25815	GUUAUUGUGAGGUAAGGCA	1435	25833	UGCCUAUCCUCAGAAUAC	3086
25833	ACUAGGUGUUAAGACUA	1436	25833	ACUAGGUGUUAAGACUA	1436	25851	UAGUCUUUAACACCCUGAGU	3087
25851	AUGUCGUUGUACAUUGGCUA	1437	25851	AUGUCGUUGUACAUUGGCUA	1437	25869	UAGCAUUGUACACGACAU	3088
25869	AUUUACCGAAGUUUACUA	1438	25869	AUUUACCGAAGUUUACUA	1438	25887	UAGUAAACUJCGGUGAAU	3089
25887	ACCAGUUGAGUCUACACA	1439	25887	ACCAGUUGAGUCUACACA	1439	25905	UGUAGACUCUACGCGUGU	3090
25905	AAUUAUACAGACACUGG	1440	25905	AAUUAUACAGACACUGG	1440	25923	CCAGUGUCUGUAGUAAUU	3091
25923	GUUUUAAAAGUUAUUAU	1441	25923	GUUUUAAAAGUUAUUAU	1441	25941	AAUUGCAUUUUUCAAUAC	3092
25941	UCUUCAUUCUUUAACAGCU	1442	25941	UCUUCAUUCUUUAACAGCU	1442	25959	AGCUUUAUUAAGUAGAA	3093
25959	UUGUUAAGACCCACCGAA	1443	25959	UUGUUAAGACCCACCGAA	1443	25977	UUCGUGGUGGUUUUAACAA	3094
25977	AUGUCAAUUAUUAUUAU	1444	25977	AUGUCAAUUAUUAUUAU	1444	25995	AUUGUGUUAUUUGCACAU	3095
25995	UCGACGGCUCUUCAGGAGU	1445	25995	UCGACGGCUCUUCAGGAGU	1445	26013	ACUCCUAGAGAGCCGUGCA	3096
26013	UUGCUAAUCCAGCAUUGGA	1446	26013	UUGCUAAUCCAGCAUUGGA	1446	26031	UCCAUUGGUGAAUAGCAA	3097
26031	AUCCAAUUUAUUAUUAU	1447	26031	AUCCAAUUUAUUAUUAU	1447	26049	GGCUCAUCAAUUAUUGAU	3098
26049	CGACGACGACUACUAGCGU	1448	26049	CGACGACGACUACUAGCGU	1448	26067	ACGCUAGUAGCUGCUGUG	3099
26067	UGCCUUUUGAAGCACAAGA	1449	26067	UGCCUUUUGAAGCACAAGA	1449	26085	UCUUGGCUUACAAAGGCA	3100
26085	AAAGUGAGUACGACUUAU	1450	26085	AAAGUGAGUACGACUUAU	1450	26103	AUAAGUUCGUACUCACUUU	3101
26103	UGUACUCUUCGUUUUGGA	1451	26103	UGUACUCUUCGUUUUGGA	1451	26121	UCCGAAACGAAUAGUACA	3102
26121	AAGAACAGGUACGUUAU	1452	26121	AAGAACAGGUACGUUAU	1452	26139	AUUAACGUACCUUUCUUU	3103
26139	UAGUUAUUAUUGCUUUCU	1453	26139	UAGUUAUUAUUGCUUUCU	1453	26157	AGAAGUAGGCUUUAUUAU	3104
26157	UUUUUUCUUGCUUUCGUGU	1454	26157	UUUUUUCUUGCUUUCGUGU	1454	26175	ACCACGAAAGCAAGAAAA	3105
26175	UAUUCUUGCUUUCGUCACU	1455	26175	UAUUCUUGCUUUCGUCACU	1455	26193	AGUGUGACUAGCAAGAAU	3106
26193	UAGCCAUCCUUCUUGGCGU	1456	26193	UAGCCAUCCUUCUUGGCGU	1456	26211	AGCGCAGUAGGAAUGGCUA	3107
26211	UUCGAAUUGUGGCGUACUG	1457	26211	UUCGAAUUGUGGCGUACUG	1457	26229	CAGUACGACACAAUUGCAA	3108
26229	GCUGCAUUAUUGUUAACGU	1458	26229	GCUGCAUUAUUGUUAACGU	1458	26247	ACGUUAACAAUUAUUGCAGC	3109
26247	UGAGUUUAUUAUUAUUAU	1459	26247	UGAGUUUAUUAUUAUUAU	1459	26265	GUUGGUUUUAUUAUUAUUAU	3110
26265	CGGUUAUUAUUAUUAUUAU	1460	26265	CGGUUAUUAUUAUUAUUAU	1460	26283	CGCGAGUAGAGUUAUUAUUAU	3111
26283	GUGUUAUUAUUAUUAUUAU	1461	26283	GUGUUAUUAUUAUUAUUAU	1461	26301	GAGUUCAGAUUUUUAUUAUUAU	3112
26301	CUUCUGAAGGAGUUAUUAU	1462	26301	CUUCUGAAGGAGUUAUUAU	1462	26319	UCAGGAACUCCUUAUUAUUAU	3113
26319	AUCUUCUGGUCUUAUUAUUAU	1463	26319	AUCUUCUGGUCUUAUUAUUAU	1463	26337	UUCGUUUAUUAUUAUUAUUAU	3114
26337	ACUUAUUAUUAUUAUUAUUAU	1464	26337	ACUUAUUAUUAUUAUUAUUAU	1464	26355	AUUAUUAUUAUUAUUAUUAU	3115

(400/110\_US)

26355	UCUGUUUUGGAACUUAUACA	1465	26355	UCUGUUUUGGAACUUAUACA	1465	26373	UGUUAAGUUUCCAAACAGA	3116
26373	AUUGCUUAUUAUUGGAGAC	1466	26373	AUUGCUUAUUAUUGGAGAC	1466	26391	GUUGCCCAUUAAGCAAU	3117
26391	CAACGGUACUUAUACCGUU	1467	26391	CAACGGUACUUAUACCGUU	1467	26409	AACGGUUAUUAAGCCGUUG	3118
26409	UGAGGAGCUUAUAAACACUC	1468	26409	UGAGGAGCUUAUAAACACUC	1468	26427	GAGUUGUUUAAGCCUCCUA	3119
26427	CCUGGAACAAUUGGAACCUA	1469	26427	CCUGGAACAAUUGGAACCUA	1469	26445	UAGGUUCCAUUUGUCCAGG	3120
26445	AGUAAUAGGUUCCUUAUC	1470	26445	AGUAAUAGGUUCCUUAUC	1470	26463	GAAUAGGAACCUUAUUAUC	3121
26463	CCUAGCCUGGAUUAUUA	1471	26463	CCUAGCCUGGAUUAUUA	1471	26481	UAAUUAUCCAGGCUAGG	3122
26481	CUAGCAUUAUUAUUAUUA	1472	26481	CUAGCAUUAUUAUUAUUA	1472	26499	AGAAUAGGCAAUUUAUUA	3123
26499	UAAUUGGAAACAGGUUUUUG	1473	26499	UAAUUGGAAACAGGUUUUUG	1473	26517	CAAAACCUUUGUCCGAUUA	3124
26517	GUACAAUUAUAAAGCUUUGU	1474	26517	GUACAAUUAUAAAGCUUUGU	1474	26535	ACAAAGCUUUAUUAUUAUC	3125
26535	UUUCCUGGCUUUGUUGG	1475	26535	UUUCCUGGCUUUGUUGG	1475	26553	CCACGAUUGCCAGAGGAAA	3126
26553	GCCAGUAAACAUUGCUUUGU	1476	26553	GCCAGUAAACAUUGCUUUGU	1476	26571	ACAAGCAAGUUAUUAUUGC	3127
26571	UUUUGUUGCUUGCUUGUC	1477	26571	UUUUGUUGCUUGCUUGUC	1477	26589	GACAGCAAGCAAGCAAAA	3128
26589	CUACAGAAUUAUUGGUG	1478	26589	CUACAGAAUUAUUGGUG	1478	26607	CACCAUUAUUAUUGUAG	3129
26607	GACUGGCGGAUUGCGAUU	1479	26607	GACUGGCGGAUUGCGAUU	1479	26625	AUUGCAUUGCCGCCAGUC	3130
26625	UGCAUUGGCUUUAUUA	1480	26625	UGCAUUGGCUUUAUUA	1480	26643	UACAAUACAAGCCAUUGCA	3131
26643	AGGUUGGCUUUGGCUUAGC	1481	26643	AGGUUGGCUUUGGCUUAGC	1481	26661	GUAAAGCCACAUAAGCCU	3132
26661	CUACUUGGCUUUGCUUUC	1482	26661	CUACUUGGCUUUGCUUUC	1482	26679	GAAGGAAGCAACGAAGUAG	3133
26679	CAGGCUUUGGCUUUGUAC	1483	26679	CAGGCUUUGGCUUUGUAC	1483	26697	GGUACGACAAACAGCCUG	3134
26697	CCGCUCAUUGGCUUUAUC	1484	26697	CCGCUCAUUGGCUUUAUC	1484	26715	GAUAGCCACAUUAGCGG	3135
26715	CAACCGAAACAAACAUU	1485	26715	CAACCGAAACAAACAUU	1485	26733	AAUUGUUGUUGGUGUUG	3136
26733	CUUCUCAUUGGCUUUC	1486	26733	CUUCUCAUUGGCUUUC	1486	26751	GAGGGCAUUAUUGAAGA	3137
26751	CCGGGGCAUUAUUGUAC	1487	26751	CCGGGGCAUUAUUGUAC	1487	26769	GGUACAAUUGUCCCGCG	3138
26769	CAGACCGCUUUGGAAAGU	1488	26769	CAGACCGCUUUGGAAAGU	1488	26787	ACUUAUAGCAAGGCUUG	3139
26787	UGAACUUGCUUUGGUGCU	1489	26787	UGAACUUGCUUUGGUGCU	1489	26805	AGCACCAGCAAGGCUUGA	3140
26805	UGUAGUACUUGGUGUAC	1490	26805	UGUAGUACUUGGUGUAC	1490	26823	GUGACCGCCAUUCGCAAG	3141
26823	CUUGCGAAUUGGCGGACAC	1491	26823	CUUGCGAAUUGGCGGACAC	1491	26841	GUGUCCGGCCAUUCGCAAG	3142
26841	CUCCCUAGGCGGCUUGAC	1492	26841	CUCCCUAGGCGGCUUGAC	1492	26859	GUCACAGCGCCUAGGGAG	3143
26859	CAUUAAGGACCUUGCCAAA	1493	26859	CAUUAAGGACCUUGCCAAA	1493	26877	UUUUGGAGGCUUUAUUG	3144
26877	AGAGUACUUGGCUUUA	1494	26877	AGAGUACUUGGCUUUA	1494	26895	UGUAGCCACAGUAGUCUCU	3145
26895	AUCACGAACGUUUCUUAU	1495	26895	AUCACGAACGUUUCUUAU	1495	26913	AUAAGAAAGCUUUGGUAU	3146
26913	UUAACAAUUAAGGCGUGC	1496	26913	UUAACAAUUAAGGCGUGC	1496	26931	CGACGCUUUAUUAUUAU	3147
26931	GCAGCGUUGGCGUACU	1497	26931	GCAGCGUUGGCGUACU	1497	26949	AUCAGUGCCUACACGCGC	3148
26949	UUCAGGUUUGGCUUUAUC	1498	26949	UUCAGGUUUGGCUUUAUC	1498	26967	GUAGCGCAAAACCCUGAA	3149
26967	CAACCGCUUUGGCUUUAUC	1499	26967	CAACCGCUUUGGCUUUAUC	1499	26985	UCCAAUAGGCUAGCGGUUG	3150
26985	AAACUUAUUAUUAUUA	1500	26985	AAACUUAUUAUUAUUA	1500	27003	UGUUAUUAUUAUUAUUA	3151
27003	AGACCCGCGGUAAGCAAC	1501	27003	AGACCCGCGGUAAGCAAC	1501	27021	GUUGCAUCCGCGGUGUUG	3152
27021	CGACAAUUAUUGCUUUA	1502	27021	CGACAAUUAUUGCUUUA	1502	27039	UAGCAAGCAUUAUUGUUG	3153
27039	AGUACGUAAGUAGCAACA	1503	27039	AGUACGUAAGUAGCAACA	1503	27057	UGUUGCACUUAUUGUACU	3154
27057	AGUAGUUAUUGCUUUA	1504	27057	AGUAGUUAUUGCUUUA	1504	27075	UCAACAGAUUAUUAUUA	3155
27075	ACUCCAGGUUAUUAUUA	1505	27075	ACUCCAGGUUAUUAUUA	1505	27093	GUUAUUAUUAUUAUUA	3156
27093	CAGAGAUUAUUAUUAUUA	1506	27093	CAGAGAUUAUUAUUAUUA	1506	27111	AUGAUUAUUAUUAUUAU	3157

(400/110\_US)

27111	UUAUGAGGACUUUACGGAU	1507	27111	UUAUGAGGACUUUACGGAU	1507	27129	AUCCUGAAAGUCCUCAUAA	3158
27129	UUGCUUUUUGGAUUCUUGA	1508	27129	UUGCUUUUUGGAUUCUUGA	1508	27147	UCAAGAUUCCAAUUAAGCAA	3159
27147	ACGUUAUAUAAGUUAUUA	1509	27147	ACGUUAUAUAAGUUAUUA	1509	27165	UUAAGAUUUAUAUAAGCGU	3160
27165	UAGUGAGACAAUAUAUUA	1510	27165	UAGUGAGACAAUAUAUUA	1510	27183	UUAUAUAUAUUGUCUCACUA	3161
27183	AGCUGACAAUAUAUAUUA	1511	27183	AGCUGACAAUAUAUAUUA	1511	27201	UUCUUCUUAUUAAGAGGCU	3162
27201	AUAUUCGGAGUUAAGAUA	1512	27201	AUAUUCGGAGUUAAGAUA	1512	27219	UCAUCUUAUUGCGAAUUAU	3163
27219	AUGAAGAACCUUAUGGAGU	1513	27219	AUGAAGAACCUUAUGGAGU	1513	27237	ACUCUUAUUGGAAUUAUUA	3164
27237	UAGAUUAUCCAAUUAUUA	1514	27237	UAGAUUAUCCAAUUAUUA	1514	27255	UCGUUUUAUUGGAAUUAUUA	3165
27255	AACAUUAUUAUUAUUAUUA	1515	27255	AACAUUAUUAUUAUUAUUA	1515	27273	AGAGAAUAUUAUUAUUAUUA	3166
27273	UUCUGACUUAUUAUUAUUA	1516	27273	UUCUGACUUAUUAUUAUUA	1516	27291	AUACAUAUAUUAUUAUUAUUA	3167
27291	UUAUUAUUAUUAUUAUUAU	1517	27291	UUAUUAUUAUUAUUAUUAU	1517	27309	AUAGCUCGCAUUAUUAUUAUUA	3168
27309	UUAUUAUUAUUAUUAUUAU	1518	27309	UUAUUAUUAUUAUUAUUAU	1518	27327	CACACUCCUUAUUAUUAUUAUUA	3169
27327	GUUAGAGGUUAUUAUUAUUA	1519	27327	GUUAGAGGUUAUUAUUAUUA	1519	27345	GUACAGUCCUUAUUAUUAUUAUUA	3170
27345	CUACUUAUUAUUAUUAUUAU	1520	27345	CUACUUAUUAUUAUUAUUAU	1520	27363	GGCAAGGUUAUUAUUAUUAUUA	3171
27363	CCAUCAGGAUAUUAUUAUUA	1521	27363	CCAUCAGGAUAUUAUUAUUA	1521	27381	CCUGUAUUAUUAUUAUUAUUA	3172
27381	GGCAUUAUUAUUAUUAUUAU	1522	27381	GGCAUUAUUAUUAUUAUUAU	1522	27399	GGUAAUAUUAUUAUUAUUAUUA	3173
27399	CCUUAUUAUUAUUAUUAUUA	1523	27399	CCUUAUUAUUAUUAUUAUUA	1523	27417	AUUAUUAUUAUUAUUAUUAUUA	3174
27417	UUUGCAUUAUUAUUAUUAUUA	1524	27417	UUUGCAUUAUUAUUAUUAUUA	1524	27435	UAGUGAAUUAUUAUUAUUAUUA	3175
27435	AGCACACUUAUUAUUAUUAUUA	1525	27435	AGCACACUUAUUAUUAUUAUUA	1525	27453	CAAAAGCAUUAUUAUUAUUAUUA	3176
27453	GUUUGUUAUUAUUAUUAUUAU	1526	27453	GUUUGUUAUUAUUAUUAUUAU	1526	27471	GAGUACCGUUAUUAUUAUUAUUA	3177
27471	CGACUUAUUAUUAUUAUUAUUA	1527	27471	CGACUUAUUAUUAUUAUUAUUA	1527	27489	GCAGUUAUUAUUAUUAUUAUUA	3178
27489	CGUGCAUUAUUAUUAUUAUUA	1528	27489	CGUGCAUUAUUAUUAUUAUUA	1528	27507	GUGAAUUAUUAUUAUUAUUAUUA	3179
27507	CCAAUUAUUAUUAUUAUUAUUA	1529	27507	CCAAUUAUUAUUAUUAUUAUUA	1529	27525	GUCUUAUUAUUAUUAUUAUUAUUA	3180
27525	CAAGAGGAGGUUAUUAUUAUUA	1530	27525	CAAGAGGAGGUUAUUAUUAUUA	1530	27543	CUUGUUAUUAUUAUUAUUAUUAUUA	3181
27543	GAGCUUAUUAUUAUUAUUAUUA	1531	27543	GAGCUUAUUAUUAUUAUUAUUA	1531	27561	AAAGUGGAGUUAUUAUUAUUAUUA	3182
27561	UUUCUUAUUAUUAUUAUUAUUA	1532	27561	UUUCUUAUUAUUAUUAUUAUUA	1532	27579	GAGCAUUAUUAUUAUUAUUAUUA	3183
27579	CUAGUUAUUAUUAUUAUUAUUA	1533	27579	CUAGUUAUUAUUAUUAUUAUUA	1533	27597	AAAGUUAUUAUUAUUAUUAUUAUUA	3184
27597	UGCUUAUUAUUAUUAUUAUUAU	1534	27597	UGCUUAUUAUUAUUAUUAUUAU	1534	27615	UUCUUAUUAUUAUUAUUAUUAUUA	3185
27615	AAGACAGAAUUAUUAUUAUUAU	1535	27615	AAGACAGAAUUAUUAUUAUUAU	1535	27633	AGCUUAUUAUUAUUAUUAUUAUUA	3186
27633	UCACUUAUUAUUAUUAUUAUUA	1536	27633	UCACUUAUUAUUAUUAUUAUUA	1536	27651	UAGAAUUAUUAUUAUUAUUAUUAUUA	3187
27651	AUUUGUUAUUAUUAUUAUUAUUA	1537	27651	AUUUGUUAUUAUUAUUAUUAUUA	1537	27669	AAGGUUAUUAUUAUUAUUAUUAUUA	3188
27669	UUUGCUUAUUAUUAUUAUUAUUA	1538	27669	UUUGCUUAUUAUUAUUAUUAUUA	1538	27687	AAACAAGGAUUAUUAUUAUUAUUA	3189
27687	UAAUUAUUAUUAUUAUUAUUAUUA	1539	27687	UAAUUAUUAUUAUUAUUAUUAUUA	1539	27705	AAUUAUUAUUAUUAUUAUUAUUAUUA	3190
27705	UUUGGUUAUUAUUAUUAUUAUUA	1540	27705	UUUGGUUAUUAUUAUUAUUAUUA	1540	27723	AUUUGGAGUUAUUAUUAUUAUUAUUA	3191
27723	UCCAGGAUUAUUAUUAUUAUUAUUA	1541	27723	UCCAGGAUUAUUAUUAUUAUUAUUA	1541	27741	GGUUAUUAUUAUUAUUAUUAUUAUUA	3192
27741	CUUGUUAUUAUUAUUAUUAUUAUUA	1542	27741	CUUGUUAUUAUUAUUAUUAUUAUUA	1542	27759	GUUUAUUAUUAUUAUUAUUAUUAUUA	3193
27759	CGAAUUAUUAUUAUUAUUAUUAUUA	1543	27759	CGAAUUAUUAUUAUUAUUAUUAUUA	1543	27777	AUGAGAGUUAUUAUUAUUAUUAUUAUUA	3194
27777	UUUGUUUAUUAUUAUUAUUAUUAUUA	1544	27777	UUUGUUUAUUAUUAUUAUUAUUAUUA	1544	27795	GAAUUAUUAUUAUUAUUAUUAUUAUUA	3195
27795	CUUAUUAUUAUUAUUAUUAUUAUUA	1545	27795	CUUAUUAUUAUUAUUAUUAUUAUUA	1545	27813	CAUUAUUAUUAUUAUUAUUAUUAUUA	3196
27813	GCACUUAUUAUUAUUAUUAUUAUUA	1546	27813	GCACUUAUUAUUAUUAUUAUUAUUA	1546	27831	CAGCGUUAUUAUUAUUAUUAUUAUUA	3197
27831	GUGCAUUAUUAUUAUUAUUAUUAUUA	1547	27831	GUGCAUUAUUAUUAUUAUUAUUAUUA	1547	27849	UGAGGUUAUUAUUAUUAUUAUUAUUA	3198
27849	AUGUGCUUAUUAUUAUUAUUAUUAUUA	1548	27849	AUGUGCUUAUUAUUAUUAUUAUUAUUA	1548	27867	CAAGGAUUAUUAUUAUUAUUAUUAUUA	3199

(400/110\_US)

27867	GUAAGGUACAACACUAGGG	1549	27867	GUAAGGUACAACACUAGGG	1549	27885	CCCUAGUGUUGUACCUUAC	3200
27885	GGUAAUACUUAUAGCACUG	1550	27885	GGUAAUACUUAUAGCACUG	1550	27903	CAGUGCUAUAAGUUAUACC	3201
27903	GUUGGCUUUGUGUCUAG	1551	27903	GUUGGCUUUGUGUCUAG	1551	27921	CUAGAGCACAAGCCCAAGC	3202
27921	GGAAGGUUUUACCUUUC	1552	27921	GGAAGGUUUUACCUUUC	1552	27939	CAAAAGUAAAACCUUUC	3203
27939	CAUAGAUGGCACUAGG	1553	27939	CAUAGAUGGCACUAGG	1553	27957	GCAAUGUGGCCAUUCUG	3204
27957	GUUCAAACAUACACCUA	1554	27957	GUUCAAACAUACACCUA	1554	27975	UAGGUGUGAUUUUGAAC	3205
27975	AUUGUACUAUACACUGUC	1555	27975	AUUGUACUAUACACUGUC	1555	27993	GACAGUUGAUUAACAUU	3206
27993	CAAGAUCCAGUGGUGUG	1556	27993	CAAGAUCCAGUGGUGUG	1556	28011	CACCACCGGGAUUCUG	3207
28011	GGCUUAUAGCUAGGUGU	1557	28011	GGCUUAUAGCUAGGUGU	1557	28029	AACACUAGCUUAAGGCG	3208
28029	UGGUACCUCAUGAAGGUC	1558	28029	UGGUACCUCAUGAAGGUC	1558	28047	GACCUCAUGAAGGUACCA	3209
28047	CACCAACUGCGCAUUA	1559	28047	CACCAACUGCGCAUUA	1559	28065	UAAUGCAGCAGUUGGUG	3210
28065	AGAGACGUACUUGUUGU	1560	28065	AGAGACGUACUUGUUGU	1560	28083	AAACAACAAGUACGUCUCU	3211
28083	UUAUAUAAACGAACAAU	1561	28083	UUAUAUAAACGAACAAU	1561	28101	AUUUGUUCGUUAUUUA	3212
28101	UAAAUGUCUAUAUUGGA	1562	28101	UAAAUGUCUAUAUUGGA	1562	28119	UCCAUUAUAGACAUUUUA	3213
28119	ACCCAAUCAAACCAACGU	1563	28119	ACCCAAUCAAACCAACGU	1563	28137	ACGUUGGUUAUUGGGU	3214
28137	UAGUGCCCGCGCAUUA	1564	28137	UAGUGCCCGCGCAUUA	1564	28155	UGUAUGCGGGGGGCAUA	3215
28155	AUUUGGUGGACCCACAGU	1565	28155	AUUUGGUGGACCCACAGU	1565	28173	AUCUGGGGUCACCAAAU	3216
28173	UUAACUGACAAUAAACAG	1566	28173	UUAACUGACAAUAAACAG	1566	28191	CUGGUUAUUGCAGUUAAG	3217
28191	GAUUGGAGGACGCAUUGG	1567	28191	GAUUGGAGGACGCAUUGG	1567	28209	CCAUUGCGUCCUCCAUUC	3218
28209	GGCAAGGCGCAACAGCGC	1568	28209	GGCAAGGCGCAACAGCGC	1568	28227	GCGCUUUUUGGCUUUGCC	3219
28227	CCGACCCCAAGGUUACCC	1569	28227	CCGACCCCAAGGUUACCC	1569	28245	GGUAACCUUUGGGUCGG	3220
28245	CAUAUAUACUGGUCUUGG	1570	28245	CAUAUAUACUGGUCUUGG	1570	28263	CUAGAGCAGUAUAUUG	3221
28263	GUUCACAGCUCACUCAG	1571	28263	GUUCACAGCUCACUCAG	1571	28281	CAGAGUGAGCUGUGAAC	3222
28281	GCAUGGCAAGGAGGAACU	1572	28281	GCAUGGCAAGGAGGAACU	1572	28299	AAGUCCUCCUUGCCUUGC	3223
28299	UAGAUUCCUUGAGGCCAG	1573	28299	UAGAUUCCUUGAGGCCAG	1573	28317	CUGCCUCCAGGGAAUCUA	3224
28317	GGCGUUCUCAAUACACCC	1574	28317	GGCGUUCUCAAUACACCC	1574	28335	GGUUGUUAUUGGAACGCC	3225
28335	CAUAUGUGUCCAGUAGC	1575	28335	CAUAUGUGUCCAGUAGC	1575	28353	GUCAUCUGGACCCAUUUG	3226
28353	CCAAUUGGCUACUACCGA	1576	28353	CCAAUUGGCUACUACCGA	1576	28371	UCGGUAGUAGCCAAUUGG	3227
28371	AAGAGCUACCCAGAGUU	1577	28371	AAGAGCUACCCAGAGUU	1577	28389	AACUGUGGUGAGCUCUU	3228
28389	UCGUGGUGUGAGCGCAA	1578	28389	UCGUGGUGUGAGCGCAA	1578	28407	UUUGCCGUCACCACCGCA	3229
28407	AUUGAAAGAGCUCAGCCC	1579	28407	AUUGAAAGAGCUCAGCCC	1579	28425	GGGCGUGAGCUCUUCAUU	3230
28425	CAGAUGUACUUAUUAAC	1580	28425	CAGAUGUACUUAUUAAC	1580	28443	GUAAUAGAUAUACCUUG	3231
28443	CCUAGGAACUGGCCAGAA	1581	28443	CCUAGGAACUGGCCAGAA	1581	28461	UUCUGGCCAGUCCUAGG	3232
28461	AGCUUACUUCUCCUAGGC	1582	28461	AGCUUACUUCUCCUAGGC	1582	28479	GCCGUAGGGAAGUAGCU	3233
28479	CGCUAACAAGAGGCAUC	1583	28479	CGCUAACAAGAGGCAUC	1583	28497	GAUGCUUUGUUAUAGCG	3234
28497	GGUAGGCUUUGCAUCUGAG	1584	28497	GGUAGGCUUUGCAUCUGAG	1584	28515	CUCAGUUGCAACCCUAGC	3235
28515	GGAGGCUUUGAAUACACC	1585	28515	GGAGGCUUUGAAUACACC	1585	28533	GGGUGUAUUAAGGCUCCC	3236
28533	CAAGACCAUUGGCACC	1586	28533	CAAGACCAUUGGCACC	1586	28551	GGUGCCAAUUGGUCUUUG	3237
28551	CCGCAUCCUUAUAACAAU	1587	28551	CCGCAUCCUUAUAACAAU	1587	28569	AUUGUAUUAAGGAUUGCGG	3238
28569	UGCUGCCACCGUACAA	1588	28569	UGCUGCCACCGUACAA	1588	28587	UUGAGCACGGUGGCAGCA	3239
28587	ACUUCUCAAAGGAACACA	1589	28587	ACUUCUCAAAGGAACACA	1589	28605	UGUUGUCCUUGAGGAAGU	3240
28605	AUUGCCAAAAGGCUUCUAC	1590	28605	AUUGCCAAAAGGCUUCUAC	1590	28623	GUAGAAGCCUUUUGGCAAU	3241

(400/110\_US)

28623	CGCAGAGGGAAGCAGAGGC	1591	28623	CGCAGAGGGAAGCAGAGGC	1591	28641	CGCAGUCAAGCCUCUUCU	1592	28641	AGAGAGGCUUCCUCUGCG	3242
28641	CGCAGUCAAGCCUCUUCU	1592	28641	CGCAGUCAAGCCUCUUCU	1592	28659	UCGUCUUAUACACGUAU	1593	28659	ACUACGUGAGGAGGCGA	3243
28659	UCGUCUUAUACACGUAU	1593	28659	UCGUCUUAUACACGUAU	1593	28677	UCGCGGUAUUAAGAAU	1594	28677	ACUUCUUAUUAACGCGA	3244
28677	UCGCGGUAUUAAGAAU	1594	28677	UCGCGGUAUUAAGAAU	1594	28695	UUAACUCCUGGAGAGU	1595	28695	ACUGUGCCAGGAGUUGA	3245
28695	UUAACUCCUGGAGAGU	1595	28695	UUAACUCCUGGAGAGU	1595	28713	UAGGGAAUUCUCCUGCU	1596	28713	AGCAGGAAUUAUCCCUA	3246
28713	UAGGGAAUUCUCCUGCU	1596	28713	UAGGGAAUUCUCCUGCU	1596	28731	UCGAUUGGCUAGGAGG	1597	28731	ACUCCGCUAGCCAUUGA	3247
28731	UCGAUUGGCUAGGAGG	1597	28731	UCGAUUGGCUAGGAGG	1597	28749	UGGUAACUGCCUCGCG	1598	28749	CGCAGGCGAUUUCACCA	3248
28749	UGGUAACUGCCUCGCG	1598	28749	UGGUAACUGCCUCGCG	1598	28767	GUUAUUGCUGUAGACAG	1599	28767	UCUGUAGCAGCAUAGC	3249
28767	GUUAUUGCUGUAGACAG	1599	28767	GUUAUUGCUGUAGACAG	1599	28785	AUUGAACCGUUGAGAGC	1600	28785	GCUCUAGCGUGGUCAAU	3250
28785	AUUGAACCGUUGAGAGC	1600	28785	AUUGAACCGUUGAGAGC	1600	28803	CAAAGUUCUGGUAAGGC	1601	28803	GCUUUAACAGAAACUUUG	3251
28803	CAAAGUUCUGGUAAGGC	1601	28803	CAAAGUUCUGGUAAGGC	1601	28821	CCAAACAACAAGGCCAA	1602	28821	UUGCCUUGUUGUUGUUGG	3252
28821	CCAAACAACAAGGCCAA	1602	28821	CCAAACAACAAGGCCAA	1602	28839	AACUGUCACUAGAAUUCU	1603	28839	AGAUUCUUAUGACAGUU	3253
28839	AACUGUCACUAGAAUUCU	1603	28839	AACUGUCACUAGAAUUCU	1603	28857	UAGCUGAGGCAUUAU	1604	28857	UUAUAGUCCUCAGCAGCA	3254
28857	UAGCUGAGGCAUUAU	1604	28857	UAGCUGAGGCAUUAU	1604	28875	AAAGCCUCGCAAAACGU	1605	28875	ACGUUUUGCGGAGGCUU	3255
28875	AAAGCCUCGCAAAACGU	1605	28875	AAAGCCUCGCAAAACGU	1605	28893	UACUGCCACAAACAGUAC	1606	28893	GUACUGUUUUGUGGCAGUA	3256
28893	UACUGCCACAAACAGUAC	1606	28893	UACUGCCACAAACAGUAC	1606	28911	CAACGUCACUAGCAUUAU	1607	28911	AAUGCUUGAGUGACGUU	3257
28911	CAACGUCACUAGCAUUAU	1607	28911	CAACGUCACUAGCAUUAU	1607	28929	UGGGAGCGUGGUCAGAA	1608	28929	UUCUGGACCCGUCUCCCA	3258
28929	UGGGAGCGUGGUCAGAA	1608	28929	UGGGAGCGUGGUCAGAA	1608	28947	ACAAACCAAGGAAUUAU	1609	28947	GAUUUCCUUGGUUUGU	3259
28947	ACAAACCAAGGAAUUAU	1609	28947	ACAAACCAAGGAAUUAU	1609	28965	CGGGACCAAGACCUAAUC	1610	28965	GAUAGGUUUUGGUCUCCG	3260
28965	CGGGACCAAGACCUAAUC	1610	28965	CGGGACCAAGACCUAAUC	1610	28983	CAGACAAGGAACUGAUUAC	1611	28983	GUAAUAGUCCUUGUUG	3261
28983	CAGACAAGGAACUGAUUAC	1611	28983	CAGACAAGGAACUGAUUAC	1611	29001	CAACAUGGCGGCAAAU	1612	29001	AAUUGCGGCAAUUGUUG	3262
29001	CAACAUGGCGGCAAAU	1612	29001	CAACAUGGCGGCAAAU	1612	29019	UGCACAUIUGCUCAAGU	1613	29019	ACUUGGACAAUUGUGCA	3263
29019	UGCACAUIUGCUCAAGU	1613	29019	UGCACAUIUGCUCAAGU	1613	29037	UGCCUGCAUUCUUUGGA	1614	29037	UCCAAAGAAUUGCAGGCA	3264
29037	UGCCUGCAUUCUUUGGA	1614	29037	UGCCUGCAUUCUUUGGA	1614	29055	AAUGUCAGCAUUGGCAUG	1615	29055	CAUGCCAAUGCGUGACAUU	3265
29055	AAUGUCAGCAUUGGCAUG	1615	29055	AAUGUCAGCAUUGGCAUG	1615	29073	GGAAGUCACACCUUCGGA	1616	29073	UCCGAAUGGUGACUUC	3266
29073	GGAAGUCACACCUUCGGA	1616	29073	GGAAGUCACACCUUCGGA	1616	29091	AACAUUGGCUAGCUUAU	1617	29091	AUGAAAGUCAGCCAUUGU	3267
29091	AACAUUGGCUAGCUUAU	1617	29091	AACAUUGGCUAGCUUAU	1617	29109	UGGAGCCAUUAAUUGGAU	1618	29109	AUCAAUUUAUUGGCUCA	3268
29109	UGGAGCCAUUAAUUGGAU	1618	29109	UGGAGCCAUUAAUUGGAU	1618	29127	UGACAAGAUCCACAAUUC	1619	29127	GAUUGGGAUUCUUUGCA	3269
29127	UGACAAGAUCCACAAUUC	1619	29127	UGACAAGAUCCACAAUUC	1619	29145	CAAAGACACGUCUACUUG	1620	29145	CAGUAGGAGUUGUUCUUG	3270
29145	CAAAGACACGUCUACUUG	1620	29145	CAAAGACACGUCUACUUG	1620	29163	GCUGAACAAAGCACAUGAC	1621	29163	GUCAAUGGCUUGUUCAGC	3271
29163	GCUGAACAAAGCACAUGAC	1621	29163	GCUGAACAAAGCACAUGAC	1621	29181	CGCAUACAAACAUUCCCA	1622	29181	UGGGAUUGUUUUGAUUGG	3272
29181	CGCAUACAAACAUUCCCA	1622	29181	CGCAUACAAACAUUCCCA	1622	29199	ACCAACAGAGCCUAAAAAG	1623	29199	CUUUUAGGCUUGUUGGU	3273
29199	ACCAACAGAGCCUAAAAAG	1623	29199	ACCAACAGAGCCUAAAAAG	1623	29217	GGACAAAAGAAAAGACU	1624	29217	AGUCUUUUUUCUUUUGUCC	3274
29217	GGACAAAAGAAAAGACU	1624	29217	GGACAAAAGAAAAGACU	1624	29235	UGAUGAAGCUCAGCCUUUG	1625	29235	CAAAGGCUAGCUUACUA	3275
29235	UGAUGAAGCUCAGCCUUUG	1625	29235	UGAUGAAGCUCAGCCUUUG	1625	29253	CGCGCAGACAAAAGAAAG	1626	29253	CUUUCUUUGUCUCUGCGGC	3276
29253	CGCGCAGACAAAAGAAAG	1626	29253	CGCGCAGACAAAAGAAAG	1626	29271	GCAGCCACUGUGACUUCU	1627	29271	AAGAGUCACAGUGGGCUGC	3277
29271	GCAGCCACUGUGACUUCU	1627	29271	GCAGCCACUGUGACUUCU	1627	29289	UCUCCUGCGGCUAGCAUG	1628	29289	CAUGUAGCCGCGAGGAAG	3278
29289	UCUCCUGCGGCUAGCAUG	1628	29289	UCUCCUGCGGCUAGCAUG	1628	29307	GGAUGAUUUCUCCAGACAA	1629	29307	UUGUCUGGAGAAUUCUCC	3279
29307	GGAUGAUUUCUCCAGACAA	1629	29307	GGAUGAUUUCUCCAGACAA	1629	29325	ACUCAAUUAUCCUAGAGU	1630	29325	ACUUAUGGAAUUAUUGAAGU	3280
29325	ACUCAAUUAUCCUAGAGU	1630	29325	ACUCAAUUAUCCUAGAGU	1630	29343	UGGAGCUUCUGUGAUUCA	1631	29343	UGAAUGGAGAAUUGGCUCA	3281
29343	UGGAGCUUCUGUGAUUCA	1631	29343	UGGAGCUUCUGUGAUUCA	1631	29361	AACUCAGGCAUAAACACUC	1632	29361	GAGUGUUUAUUGCCUGAGUU	3282
29361	AACUCAGGCAUAAACACUC	1632	29361	AACUCAGGCAUAAACACUC	1632						3283

(400/110\_US)

29379	CAUGAUGACCACACAAAGGC	1633	29379	CAUGAUGACCACACAAAGGC	1633	29397	GCCTUUGUGUGGUAUUAUG	3284
29397	CAGAUUGGGUAUUAACG	1634	29397	CAGAUUGGGUAUUAACG	1634	29415	CGUUUACAUAGCCCAUUG	3285
29415	GUUUUGCAUUAUCCGUUA	1635	29415	GUUUUGCAUUAUCCGUUA	1635	29433	UAAACGGAUUGCGAAAC	3286
29433	ACGAUACAUAGUCUACUCU	1636	29433	ACGAUACAUAGUCUACUCU	1636	29451	AGAGUAGACAUUGUAGGU	3287
29451	UUGUGCAGAUAUUAUUCUC	1637	29451	UUGUGCAGAUAUUAUUCUC	1637	29469	GAGAAUUAUUAUUGCACA	3288
29469	CGUAACUAACAGCACAAG	1638	29469	CGUAACUAACAGCACAAG	1638	29487	CUUGUGUGUUAUUAUAGC	3289
29487	GUAGGUUAUUAUUAUUAU	1639	29487	GUAGGUUAUUAUUAUUAU	1639	29505	UAAAGUUAACUAAACCUAC	3290
29505	AUUCACAUAGCAUUAU	1640	29505	AUUCACAUAGCAUUAU	1640	29523	AAGAUUGCUAUGUGAGAUU	3291
29523	UUAUUAUUAUUAUUAUUA	1641	29523	UUAUUAUUAUUAUUAUUA	1641	29541	AAUUAUUAUUAUUAUUA	3292
29541	UAGGGAGGACUUAUUAAG	1642	29541	UAGGGAGGACUUAUUAAG	1642	29559	CUUUUUAUUAUUAUUA	3293
29559	GCCACCAUUAUUAUUAUUA	1643	29559	GCCACCAUUAUUAUUAUUA	1643	29577	UCGAUGAAAUUGUGGUGGC	3294
29577	AGGCCACGCGGAGUACGAU	1644	29577	AGGCCACGCGGAGUACGAU	1644	29595	AUCGUACUCCGUGGUGCCU	3295
29595	UCGAGGGUACAGUUAUUA	1645	29595	UCGAGGGUACAGUUAUUA	1645	29613	UUAUUAUUAUUAUUAUUA	3296
29613	AUGCUAGGGAGGAGCUGCCU	1646	29613	AUGCUAGGGAGGAGCUGCCU	1646	29631	AGGCAUGCUCUCCUAGCAU	3297
29631	UUAUUGGAAGGCCUUAU	1647	29631	UUAUUGGAAGGCCUUAU	1647	29649	AUAAGGGCUUUAUUAUUA	3298
29649	UGUGUAAAUUAUUAUUAU	1648	29649	UGUGUAAAUUAUUAUUAU	1648	29667	CUAAAUUAUUAUUAUUA	3299
29667	GUAGUGCUAUCUCCCAUGUG	1649	29667	GUAGUGCUAUCUCCCAUGUG	1649	29685	CACAUUGGGUAUUAUUAU	3300
29685	GAUUAUUAUUAUUAUUAU	1650	29685	GAUUAUUAUUAUUAUUAU	1650	29703	CUAAGAAAGCUUUAUUAU	3301
29703	GGAGAAUGACAAAAA	1651	29703	GGAGAAUGACAAAAA	1651	29721	UUUUUUUUUGUCAUUAUCC	3302

The 3'-ends of the Upper sequence and the Lower sequence of the siNA construct can include an overhang sequence, for example about 1, 2, 3, or 4 nucleotides in length, preferably 2 nucleotides in length, wherein the overhanging sequence of the lower sequence is optionally complementary to a portion of the target sequence. The overhang can comprise the general structure B, BNN, NN, BNNs, or NsN, where B stands for any terminal cap moiety, N stands for any nucleotide (e.g., thymidine) and s stands for phosphorothioate or other internucleotide linkage as described herein (e.g. internucleotide linkage having Formula I). The upper sequence is also referred to as the sense strand, whereas the lower sequence is also referred to as the antisense strand. The upper and lower sequences in the Table can further comprise a chemical modification having Formulae I-VII or any combination thereof (see for example chemical modifications as shown in Table V herein).



(400/110\_US)

Table III: SARS synthetic siRNA and Target Sequences

Target Pos	Target	SeqID	RPI#	Aliases	Sequence	SeqID
1655	UGAUGAAGAGGUGGCCAUCAUU	3303		SARS:1657U21 siRNA sense	AAUGAAGAGGUGGCCAUCATT	3311
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1166U21 siRNA sense	UUGCAUCUCCACAGGAGUGTT	3312
2381	CUCAAAGCAAGGACUUAUACCGU	3305		SARS:2383U21 siRNA sense	CAAAGCAAGGACUUAUACCTT	3313
2598	CUGUGUAAUUGGCCUUAUACCGU	3306		SARS:2600U21 siRNA sense	GUGUAAUUGGCCUUAUACCTT	3314
26572	UUUGUCUUGGUGGUGGUGGUGUACAG	3307		SARS:26574U21 siRNA sense	UUUGUCUUGGUGGUGGUGUACCTT	3315
26790	ACUUGUCAUUGGUGGUGGUGGUGAUA	3308		SARS:26792U21 siRNA sense	UUUGUCAUUGGUGGUGGUGAUTT	3316
26786	UUGAACCAAGCUUGAGAGGCAAGU	3309		SARS:26788U21 siRNA sense	GAACCAAGCUUGAGAGGCAAAATT	3317
26529	GCUUGUUUCCUCUGGCGUCUUGU	3310		SARS:26531U21 siRNA sense	UUGUUUCCUCUGGCGUCUUTT	3318
1655	UGAUGAAGAGGUGGCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) antisense	UGAUGGCAACCUCUUAUUAUTT	3319
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) antisense	CACUCCUGUGGAGAUUGCAATT	3320
2381	CUCAAAGCAAGGACUUAUACCGU	3305		SARS:2401L21 siRNA (2383C) antisense	GGUAAAAGUCCCUUGCUUUGTT	3321
2598	CUGUGUAAUUGGCCUUAUACCGU	3306		SARS:2618L21 siRNA (2600C) antisense	AGCAUGAGGCCCAUUAUACACTT	3322
26572	UUUGUCUUGGUGGUGGUGGUGUACAG	3307		SARS:26592L21 siRNA (26574C) antisense	GUAGACAGCAGCAAGCACACTT	3323
26790	ACUUGUCAUUGGUGGUGGUGAUA	3308		SARS:26810L21 siRNA (26792C) antisense	AUCACAGCACCAAUUGACAATT	3324
26786	UUGAACCAAGCUUGAGAGGCAAGU	3309		SARS:26806L21 siRNA (26788C) antisense	UUUGCUCUCAAGCUGGUUUCTT	3325
26529	GCUUGUUUCCUCUGGCGUCUUGU	3310		SARS:26549L21 siRNA (26531C) antisense	AAGAGCCAGAGGAAACCAATT	3326
1655	UGAUGAAGAGGUGGCCAUCAUU	3303		SARS:1657U21 siRNA stab04 sense	B AAUGAAGAGGUGGCCAUCATT B	3327
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1166U21 siRNA stab04 sense	B UUUGCAUCUCCACAGGAGUGTT B	3328
2381	CUCAAAGCAAGGACUUAUACCGU	3305		SARS:2383U21 siRNA stab04 sense	B CAAAAGCAAGGACUUUAUACCTT B	3329
2598	CUGUGUAAUUGGCCUUAUACCGU	3306		SARS:2600U21 siRNA stab04 sense	B GUUAAAUUGGCCUUAUACCTT B	3330
26572	UUUGUCUUGGUGGUGGUGGUGUACAG	3307		SARS:26574U21 siRNA stab04 sense	B UUUGUCUUGGUGGUGGUGUACCTT B	3331
26790	ACUUGUCAUUGGUGGUGGUGAUA	3308		SARS:26792U21 siRNA stab04 sense	B UUUGUCAUUGGUGGUGGUGAUTT B	3332
26786	UUGAACCAAGCUUGAGAGGCAAGU	3309		SARS:26788U21 siRNA stab04 sense	B GAAACCAAGCUUGAGAGGCAAAATT B	3333
26529	GCUUGUUUCCUCUGGCGUCUUGU	3310		SARS:26531U21 siRNA stab04 sense	B UUUGUUUCCUCUGGCGUCUUTT B	3334
1655	UGAUGAAGAGGUGGCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) antisense	UGAUGGCAACCUCUUAUUAUTT	3335
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) antisense	CACUCCUGUGGAGAUUGCAATT	3336

(400/110\_US)

2381	CUCAAAGCAAGGGACUUAUACCGU	3305	SARS:2401L21 siRNA (2383C) stab05 antisense	GGUAAAAGGuccuuGcuuGTsT	3337
2598	CUGUGUAAAUGGCCUCAUGCUU	3306	SARS:2618L21 siRNA (2600C) stab05 antisense	AGCAUGAGGccAuuuAcAcTsT	3338
26572	UUUGUCUUGCUGCUGUCUACAG	3307	SARS:26592L21 siRNA (26574C) stab05 antisense	GUAGACAGcAGcAAGcAcATsT	3339
26790	ACUUGUCAUUGGUGCUGUGAUA	3308	SARS:26810L21 siRNA (26792C) stab05 antisense	AucAcAGcAccAAuGAcAAATsT	3340
28786	UUGAACcAGCUUGAGAGCAAAGU	3309	SARS:28806L21 siRNA (28788C) stab05 antisense	uuuGcucucAAAGcuGGuucTsT	3341
26529	GCUUGUUUCCUCUGGCUCUUGU	3310	SARS:26549L21 siRNA (26531C) stab05 antisense	AAGAGccAGAGGAAAcAAATsT	3342
1655	UGAAUGAAGAGGUUGCCAUAU	3303	SARS:1657U21 siRNA stab07 sense	B AAUGAAAGAGGuuGccAuCATT B	3343
1164	UGUUGCAUCCACAGGAGUGUA	3304	SARS:1166U21 siRNA stab07 sense	B uuGcAuucuccAcAGGAGUGTT B	3344
2381	CUCAAAGCAAGGGACUUAUACCGU	3305	SARS:2383U21 siRNA stab07 sense	B cAAAAGcAAGGGAGcuuuAccTT B	3345
2598	CUGUGUAAAUGGCCUCAUGCUU	3306	SARS:2600U21 siRNA stab07 sense	B GuGuAAAUuGGccuAuGcuTT B	3346
26572	UUUGUCUUGCUGCUGUCUACAG	3307	SARS:2657U21 siRNA stab07 sense	B uuGcAuuuGcuGcuGcuAcTT B	3347
26790	ACUUGUCAUUGGUGCUGUGAUA	3308	SARS:26792U21 siRNA stab07 sense	B uuGcAuuuGcuGcuGcuGcuATT B	3348
28786	UUGAACcAGCUUGAGAGCAAAGU	3309	SARS:28788U21 siRNA stab07 sense	B GAAccAGuuGAGAGcAAATT B	3349
26529	GCUUGUUUCCUCUGGCUCUUGU	3310	SARS:26531U21 siRNA stab07 sense	B uuGuuuuccuGcGcuuuTT B	3350
1655	UGAAUGAAGAGGUUGCCAUAU	3303	SARS:1675L21 siRNA (1657C) stab11 antisense	uGAUGGcAAccucuuAuTTsT	3351
1164	UGUUGCAUCCACAGGAGUGUA	3304	SARS:1184L21 siRNA (1166C) stab11 antisense	cAcuccuGuGGAGAuGcAAATsT	3352
2381	CUCAAAGCAAGGGACUUAUACCGU	3305	SARS:2401L21 siRNA (2383C) stab11 antisense	GGUAAAAGGuccuuGcuuGTsT	3353
2598	CUGUGUAAAUGGCCUCAUGCUU	3306	SARS:2618L21 siRNA (2600C) stab11 antisense	AGcAuGAGGccAuuuAcAcTsT	3354
26572	UUUGUCUUGCUGCUGUCUACAG	3307	SARS:26592L21 siRNA (26574C) stab11 antisense	GUAGACAGcAGcAAGcAcATsT	3355
26790	ACUUGUCAUUGGUGCUGUGAUA	3308	SARS:26810L21 siRNA (26792C) stab11 antisense	AucAcAGcAccAAuGAcAAATsT	3356
28786	UUGAACcAGCUUGAGAGCAAAGU	3309	SARS:28806L21 siRNA (28788C) stab11 antisense	uuuGcucucAAAGcuGGuucTsT	3357
26529	GCUUGUUUCCUCUGGCUCUUGU	3310	SARS:26549L21 siRNA (26531C) stab11 antisense	AAGAGccAGAGGAAAcAAATsT	3358
1655	UGAAUGAAGAGGUUGCCAUAU	3303	SARS:1657U21 siRNA stab08 sense	AAUGAAAGAGGuuGccAuCATsT	3359
1164	UGUUGCAUCCACAGGAGUGUA	3304	SARS:1166U21 siRNA stab08 sense	uuGcAuucuccAcAGGAGUGTTsT	3360
2381	CUCAAAGCAAGGGACUUAUACCGU	3305	SARS:2383U21 siRNA stab08 sense	cAAAGcAAGGGAGcuuuAccTsT	3361
2598	CUGUGUAAAUGGCCUCAUGCUU	3306	SARS:2600U21 siRNA stab08 sense	GuGuAAAuGGccuAuGcuTTsT	3362



(400/110\_US)

26572	UUUGUGCUUUGGUGGUGUCUACAG	3307		SARS:26574U21 siRNA stab08 sense	uGuGcuuGcuGcuGucuaCTsT	3363
26790	ACUUGUCAUUGGUGGUGUGAUA	3308		SARS:26792U21 siRNA stab08 sense	uuGucAuuuGGuGcuGUGAUTsT	3364
28786	UUGAACCGAGCUUGAGAGCAAAGU	3309		SARS:28788U21 siRNA stab08 sense	GAAccAGcuuGAGAGCAAATsT	3365
26529	GCUUGUUUCCUCUGGCGUCUUGU	3310		SARS:26531U21 siRNA stab08 sense	uuGuuuuuccucuGGcucuTtsT	3366
1655	UGAAUGAAGAGGUUGCCAUAUU	3303		SARS:1675L21 siRNA (1657C) stab08 antisense	uGAUGGcAAccucuucAuutTsT	3367
1164	UGUUGCAUCUCCACAGAGUGUA	3304		SARS:1184L21 siRNA (1166C) stab08 antisense	cAcuccuGuGGAGAuGcAAATsT	3368
2381	CUCAAAGCAAGGGACUUAUACCGU	3305		SARS:2401L21 siRNA (2383C) stab08 antisense	GGuAAAAGucccuuGcuuuGTsT	3369
2598	CUGUGUAAUUGGCCUCAUGCUCU	3306		SARS:2618L21 siRNA (2600C) stab08 antisense	AGcAUAGAGGccAuuuAcAcTsT	3370
26572	UUUGUGCUUUGGUGGUGUCUACAG	3307		SARS:26592L21 siRNA (26574C) stab08 antisense	GuAGAcAGcAGcAAAGcAcATsT	3371
26790	ACUUGUCAUUGGUGGUGUGAUA	3308		SARS:26810L21 siRNA (26782C) stab08 antisense	AucAcAGcAccAAUgAcAAATsT	3372
28786	UUGAACCGAGCUUGAGAGCAAAGU	3309		SARS:28806L21 siRNA (28788C) stab08 antisense	uuuGcucucAAAGcuGGuucTsT	3373
26529	GCUUGUUUCCUCUGGCGUCUUGU	3310		SARS:26549L21 siRNA (26531C) stab08 antisense	AAGAGccAGAGGAAACAAATsT	3374

Uppercase = ribonucleotide  
 u,c = 2'-deoxy-2'-fluoro U, C  
 A = 2'-O-methyl Adenosine  
 G = 2'-O-methyl Guanosine  
 T = thymidine  
 B = inverted deoxy abasic  
 s = phosphorothioate linkage  
 A = deoxy Adenosine  
 G = deoxy Guanosine

Table IV

Non-limiting examples of Stabilization Chemistries for chemically modified siNA constructs

Chemistry	pyrimidine	Purine	cap	p=S	Strand
"Stab 00"	Ribo	Ribo	TT at 3'-ends		S/AS
"Stab 1"	Ribo	Ribo	-	5 at 5'-end 1 at 3'-end	S/AS
"Stab 2"	Ribo	Ribo	-	All linkages	Usually AS
"Stab 3"	2'-fluoro	Ribo	-	4 at 5'-end 4 at 3'-end	Usually S
"Stab 4"	2'-fluoro	Ribo	5' and 3'-ends	-	Usually S
"Stab 5"	2'-fluoro	Ribo	-	1 at 3'-end	Usually AS
"Stab 6"	2'-O-Methyl	Ribo	5' and 3'-ends	-	Usually S
"Stab 7"	2'-fluoro	2'-deoxy	5' and 3'-ends	-	Usually S
"Stab 8"	2'-fluoro	2'-O-Methyl	-	1 at 3'-end	Usually AS
"Stab 9"	Ribo	Ribo	5' and 3'-ends	-	Usually S
"Stab 10"	Ribo	Ribo	-	1 at 3'-end	Usually AS
"Stab 11"	2'-fluoro	2'-deoxy	-	1 at 3'-end	Usually AS
"Stab 12"	2'-fluoro	LNA	5' and 3'-ends		Usually S
"Stab 13"	2'-fluoro	LNA		1 at 3'-end	Usually AS
"Stab 14"	2'-fluoro	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 15"	2'-deoxy	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 16"	Ribo	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 17"	2'-O-Methyl	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 18"	2'-fluoro	2'-O-Methyl	5' and 3'-ends	1 at 3'-end	Usually S
"Stab 19"	2'-fluoro	2'-O-Methyl	3'-end		Usually AS
"Stab 20"	2'-fluoro	2'-deoxy	3'-end		Usually AS
"Stab 21"	2'-fluoro	Ribo	3'-end		Usually AS
"Stab 22"	Ribo	Ribo	3'-end -		Usually AS

CAP = any terminal cap, see for example Figure 10.

All Stab 1-22 chemistries can comprise 3'-terminal thymidine (TT) residues

All Stab 1-22 chemistries typically comprise about 21 nucleotides, but can vary as described herein.

S = sense strand

AS = antisense strand

Table V

A. 25  $\mu$ mol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	6.5	163 $\mu$ L	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 $\mu$ L	45 sec	2.5 min	7.5 min
Acetic Anhydride	100	233 $\mu$ L	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 $\mu$ L	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	645 $\mu$ L	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2  $\mu$ mol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	15	31 $\mu$ L	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 $\mu$ L	45 sec	233 min	465 sec
Acetic Anhydride	655	124 $\mu$ L	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 $\mu$ L	5 sec	5 sec	5 sec
TCA	700	732 $\mu$ L	10 sec	10 sec	10 sec
Iodine	20.6	244 $\mu$ L	15 sec	15 sec	15 sec
Beaucage	7.7	232 $\mu$ L	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2  $\mu$ mol Synthesis Cycle 96 well Instrument

Reagent	Equivalents:DNA/ 2'-O-methyl/Ribo	Amount: DNA/2'-O- methyl/Ribo	Wait Time* DNA	Wait Time* 2'-O- methyl	Wait Time* Ribo
Phosphoramidites	22/33/66	40/60/120 $\mu$ L	60 sec	180 sec	360sec
S-Ethyl Tetrazole	70/105/210	40/60/120 $\mu$ L	60 sec	180 min	360 sec
Acetic Anhydride	265/265/265	50/50/50 $\mu$ L	10 sec	10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 $\mu$ L	10 sec	10 sec	10 sec
TCA	238/475/475	250/500/500 $\mu$ L	15 sec	15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 $\mu$ L	30 sec	30 sec	30 sec
Beaucage	34/51/51	80/120/120	100 sec	200 sec	200 sec
Acetonitrile	NA	1150/1150/1150 $\mu$ L	NA	NA	NA

- 5
- Wait time does not include contact time during delivery.
  - Tandem synthesis utilizes double coupling of linker molecule

CLAIMS

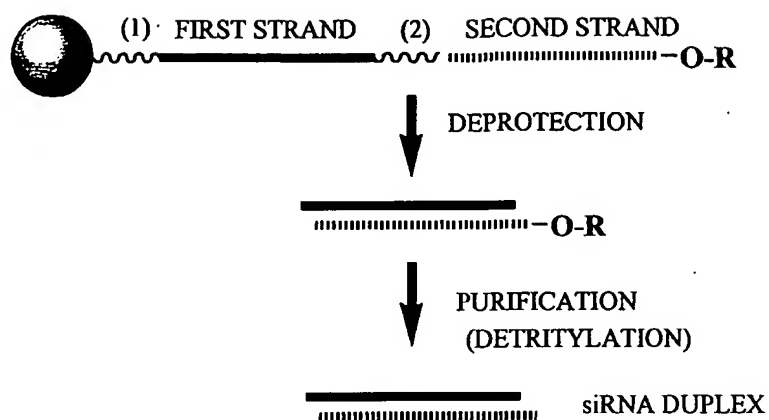
What we claim is:

1. A chemically synthesized double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a severe acute respiratory syndrome (SARS) virus RNA via RNA interference, wherein:
  - a. each strand of said siNA molecule is about 19 to about 23 nucleotides in length;
  - b. one strand of said siNA molecule comprises nucleotide sequence having sufficient complementarity to said SARS virus RNA for the siNA molecule to direct cleavage of the SARS virus RNA via RNA interference; and
  - c. said siNA molecule does not require the presence of nucleotides having a 2'-hydroxy group for mediating RNA interference.
2. The siNA molecule of claim 1, wherein said siNA molecule comprises no ribonucleotides.
3. The siNA molecule of claim 1, wherein said siNA molecule comprises ribonucleotides.
4. The siNA molecule of claim 1, wherein one strand of said double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein a second strand of said double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of said SARS virus RNA.
5. The siNA molecule of claim 4, wherein each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and wherein each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand.
6. The siNA molecule of claim 1, wherein said siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein said siNA further comprises a sense region, wherein said sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of said SARS virus gene or a portion thereof.

7. The siNA molecule of claim 6, wherein said antisense region and said sense region comprises about 19 to about 23 nucleotides, and wherein said antisense region comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region.
- 5 8. The siNA molecule of claim 1, wherein said siNA molecule comprises a sense region and an antisense region, and wherein said antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS virus gene, or a portion thereof, and said sense region comprises a nucleotide sequence that is complementary to said antisense region.
- 10 9. The siNA molecule of claim 6, wherein said siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region of said siNA molecule.
10. The siNA molecule of claim claim 6, wherein said sense region is connected to the antisense region via a linker molecule.
- 15 11. The siNA molecule of claim 10, wherein said linker molecule is a polynucleotide linker.
12. The siNA molecule of claim 10, wherein said linker molecule is a non-nucleotide linker.
13. The siNA molecule of claim 6, wherein pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine nucleotides.
- 20 14. The siNA molecule of claim 6, wherein purine nucleotides in the sense region are 2'-deoxy purine nucleotides.
15. The siNA molecule of claim 6, wherein pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
- 25 16. The siNA molecule of claim 9, wherein the fragment comprising said sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment comprising said sense region.
17. The siNA molecule of claim 16, wherein said terminal cap moiety is an inverted deoxy abasic moiety.
- 30 18. The siNA molecule of claim 6, wherein pyrimidine nucleotides of said antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides

19. The siNA molecule of claim 6, wherein purine nucleotides of said antisense region are 2'-O-methyl purine nucleotides.
20. The siNA molecule of claim 6, wherein purine nucleotides present in said antisense region comprise 2'-deoxy- purine nucleotides.
- 5 21. The siNA molecule of claim 18, wherein said antisense region comprises a phosphorothioate internucleotide linkage at the 3' end of said antisense region.
22. The siNA molecule of claim 6, wherein said antisense region comprises a glyceryl modification at the 3' end of said antisense region.
- 10 23. The siNA molecule of claim 9, wherein each of the two fragments of said siNA molecule comprise 21 nucleotides.
24. The siNA molecule of claim 23, wherein about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other  
15 fragment of the siNA molecule.
25. The siNA molecule of claim 24, wherein each of the two 3' terminal nucleotides of each fragment of the siNA molecule are 2'-deoxy-pyrimidines.
26. The siNA molecule of claim 25, wherein said 2'-deoxy-pyrimidine is 2'-deoxy-thymidine.
- 20 27. The siNA molecule of claim 23, wherein all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule.
28. The siNA molecule of claim 23, wherein about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.  
25
29. The siNA molecule of claim 23, wherein 21 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.
30. The siNA molecule of claim 9, wherein the 5'-end of the fragment comprising said  
30 antisense region optionally includes a phosphate group.

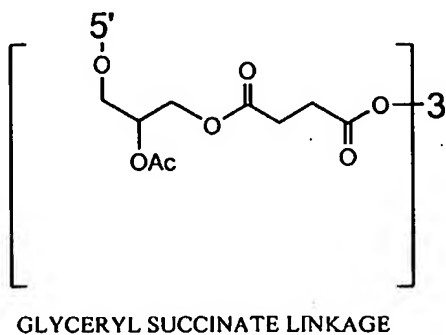
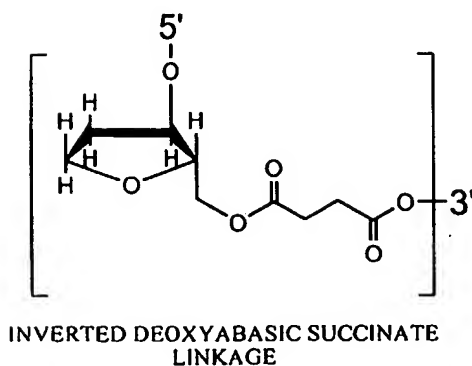
31. A pharmaceutical composition comprising the siNA molecule of claim 1 in an acceptable carrier or diluent.

*Figure 1*

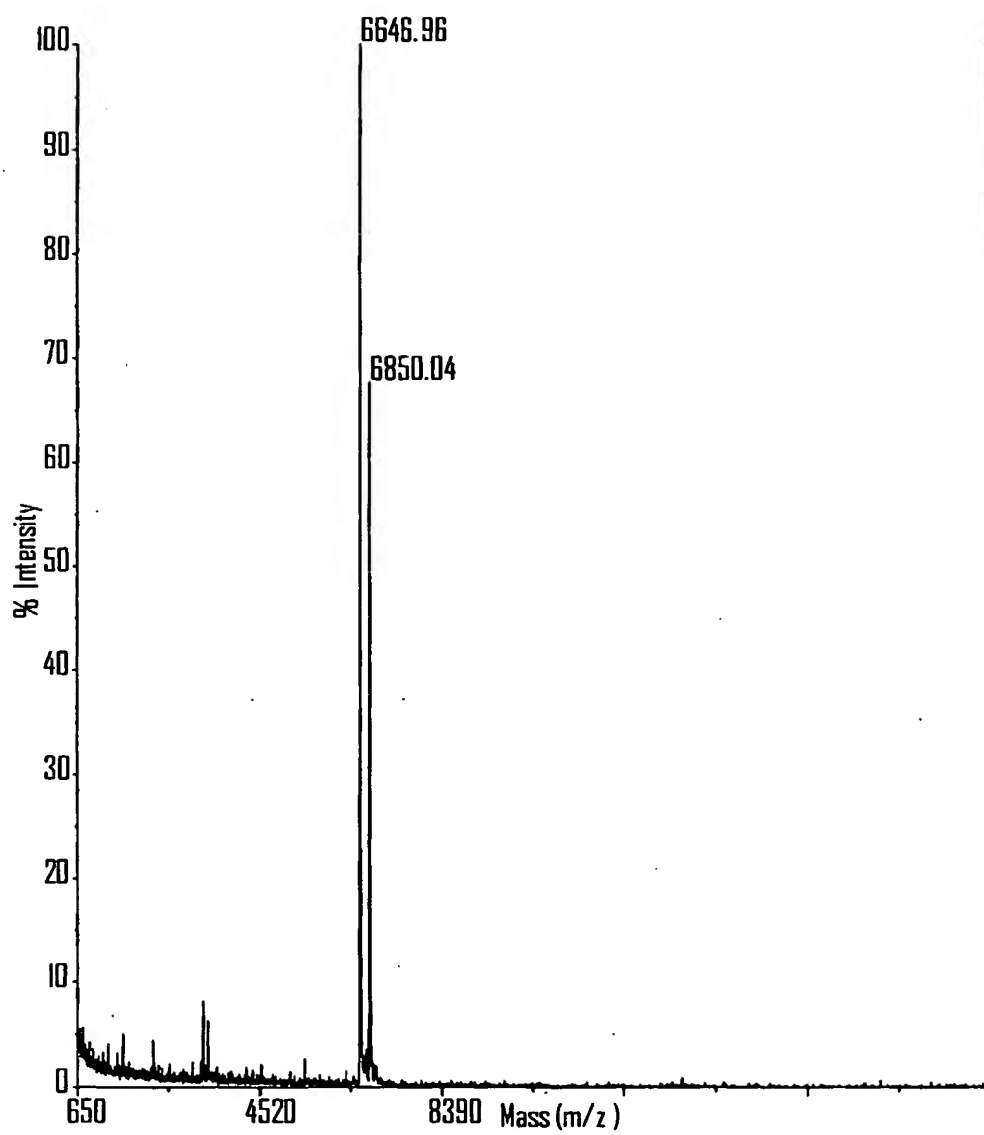
= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP  
 FOR EXAMPLE:  
 DIMETHOXYTRITYL (DMT)

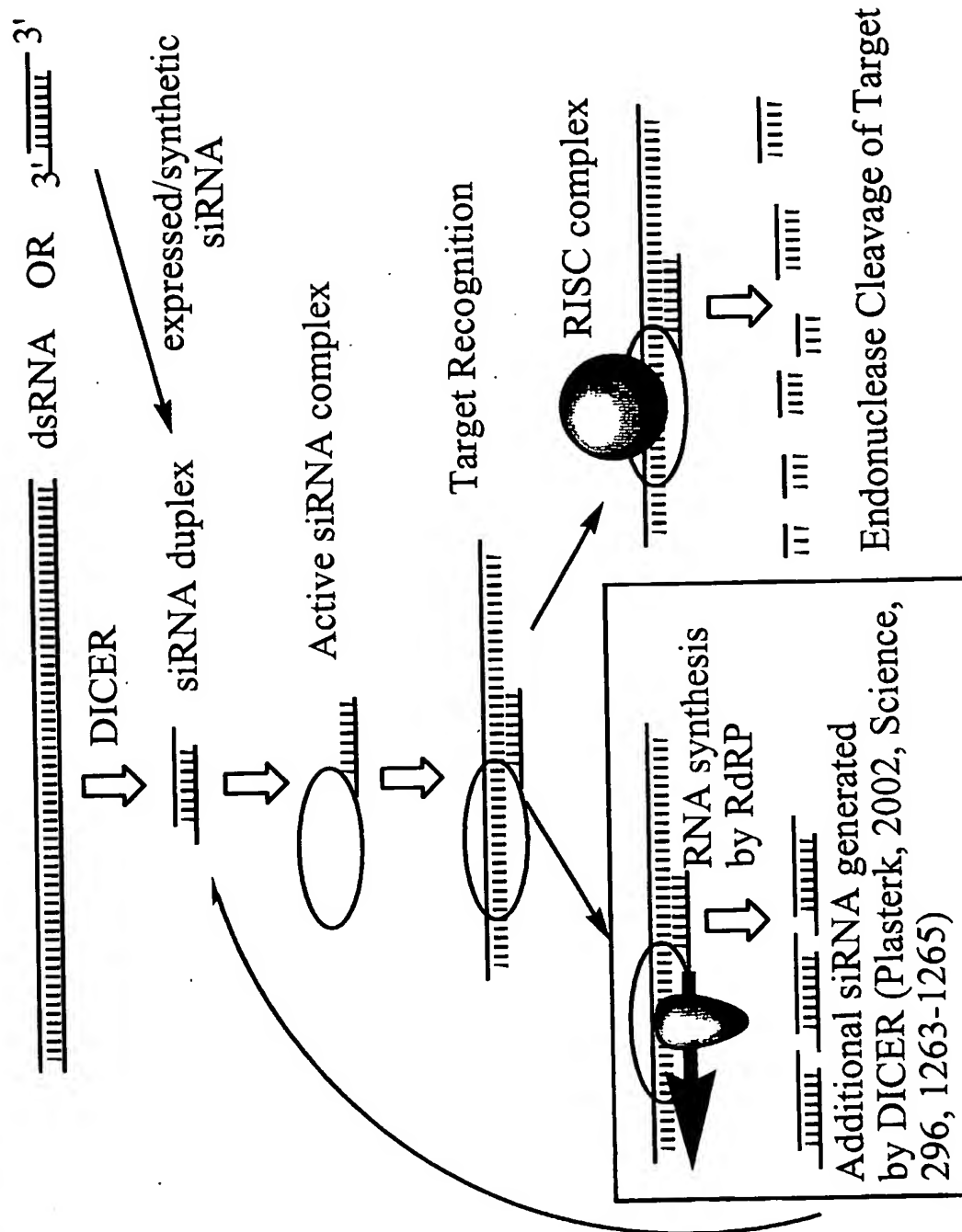
(1) = CLEAVABLE LINKER  
 (FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR  
 INVERTED DEOXYABASIC SUCCINATE)  
 (2) = CLEAVABLE LINKER  
 (FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR  
 INVERTED DEOXYABASIC SUCCINATE)

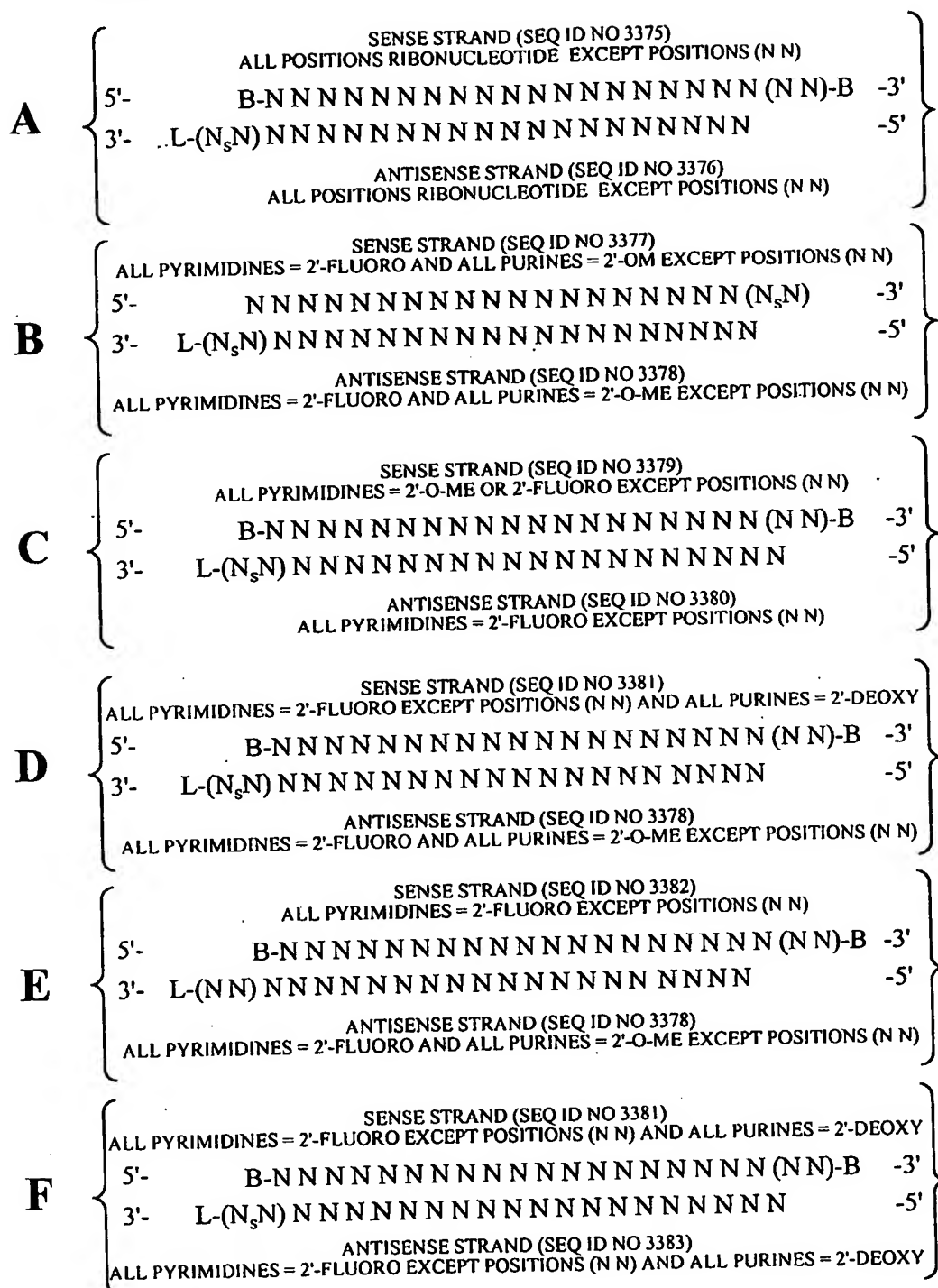




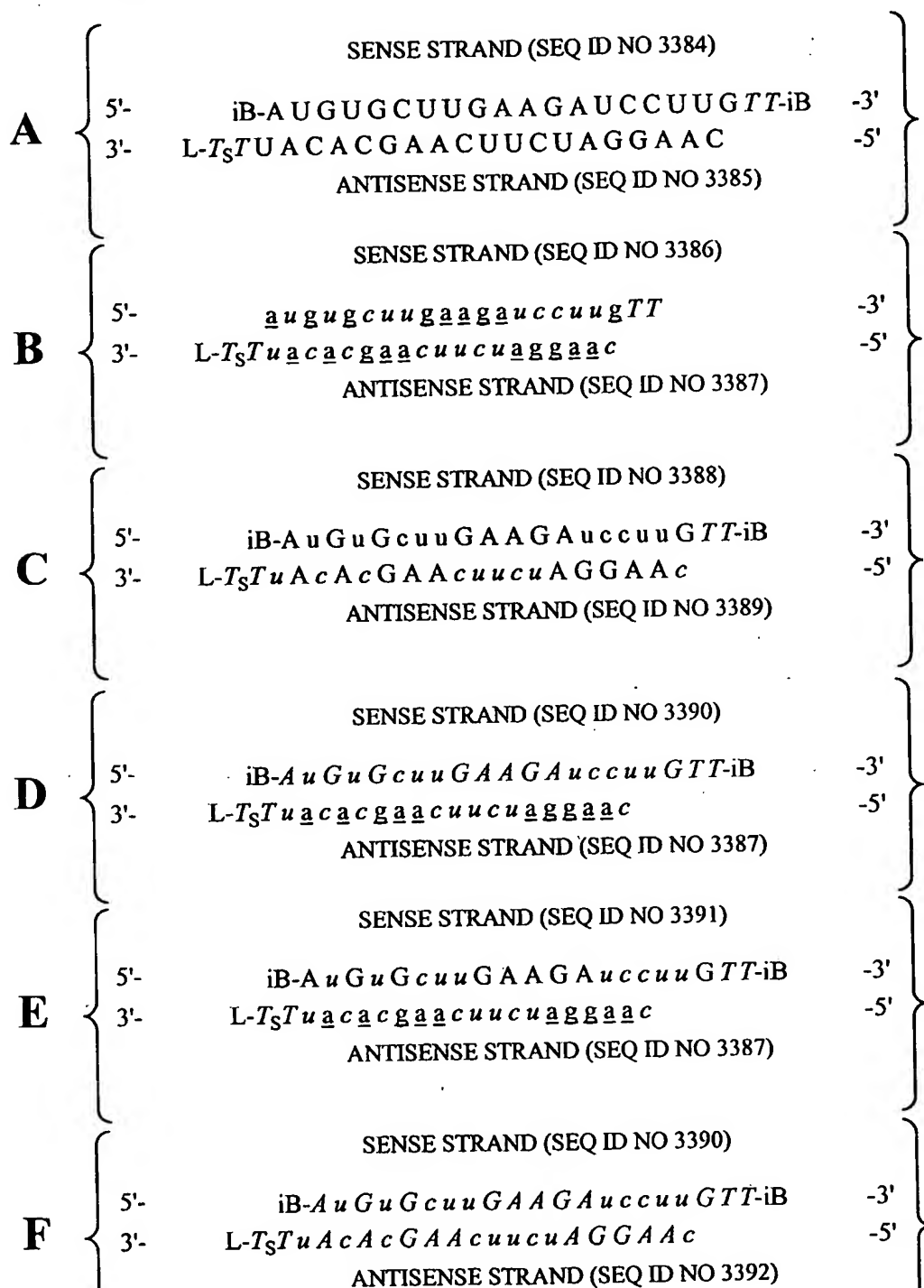
*Figure 2*

**Figure 3**



**Figure 4**

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENTL = GLYCERYL or B THAT IS OPTIONALLY PRESENTS = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionally absent

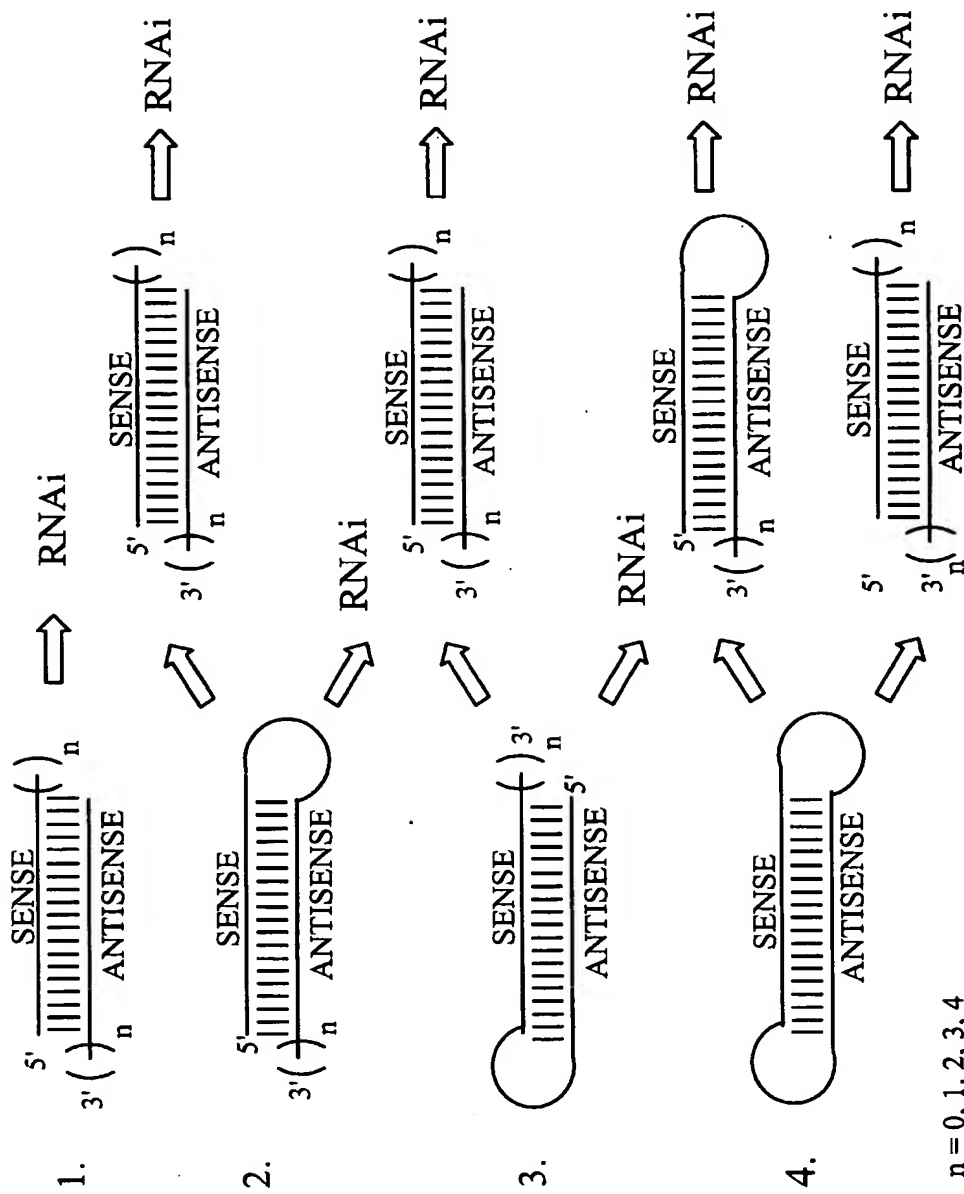
**Figure 5**

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro

*italic lower case* = 2'-deoxy-2'-fluorounderline = 2'-O-methyl

ITALIC UPPER CASE = DEOXYIB = INVERTED  
DEOXYABASICL = GLYCERYL MOIETY or iB  
OPTIONALLY PRESENTS = PHOSPHOROTHIOATE (C  
PHOSPHORODITHIOATE OPTIONALLY PRESEN

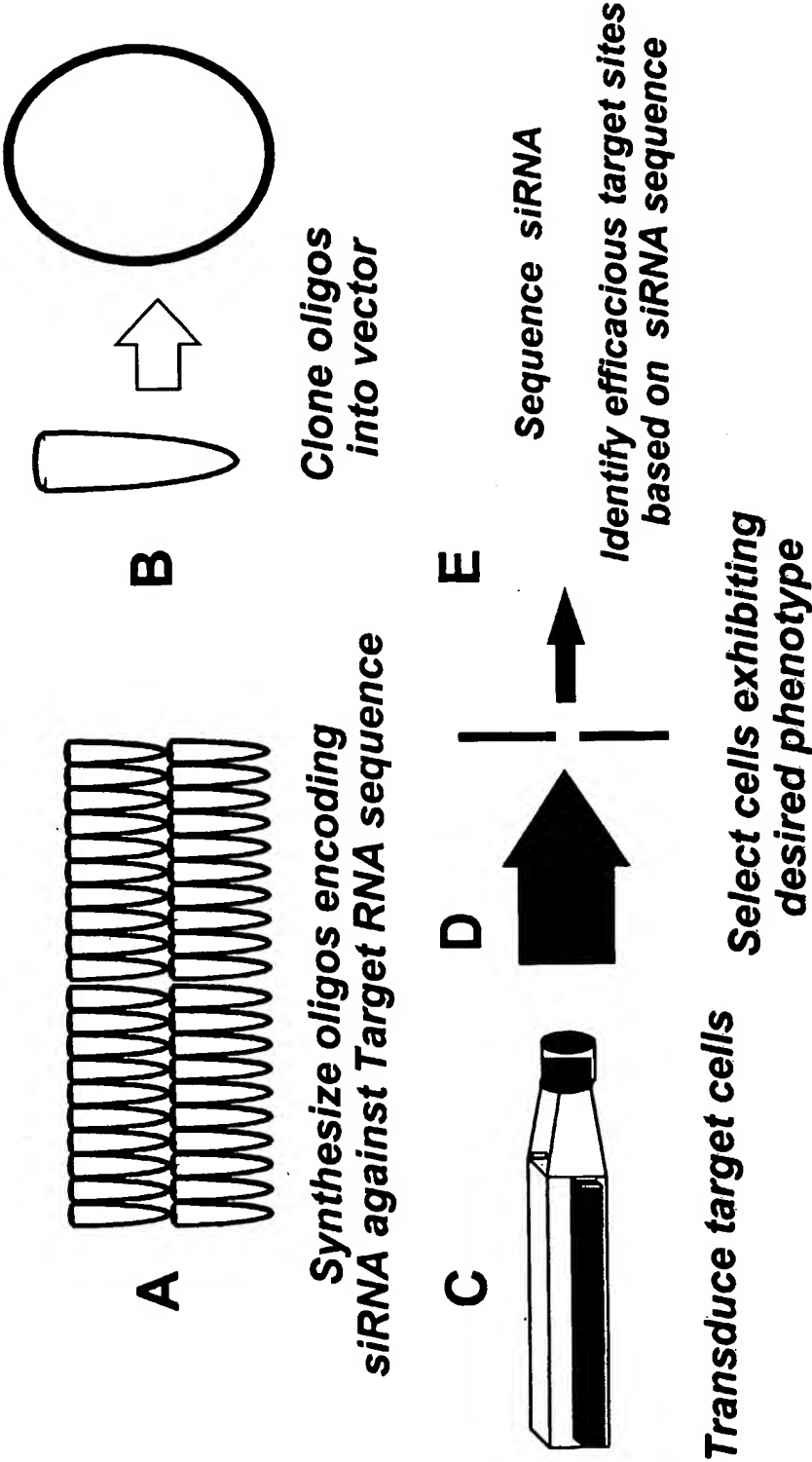
Figure 6



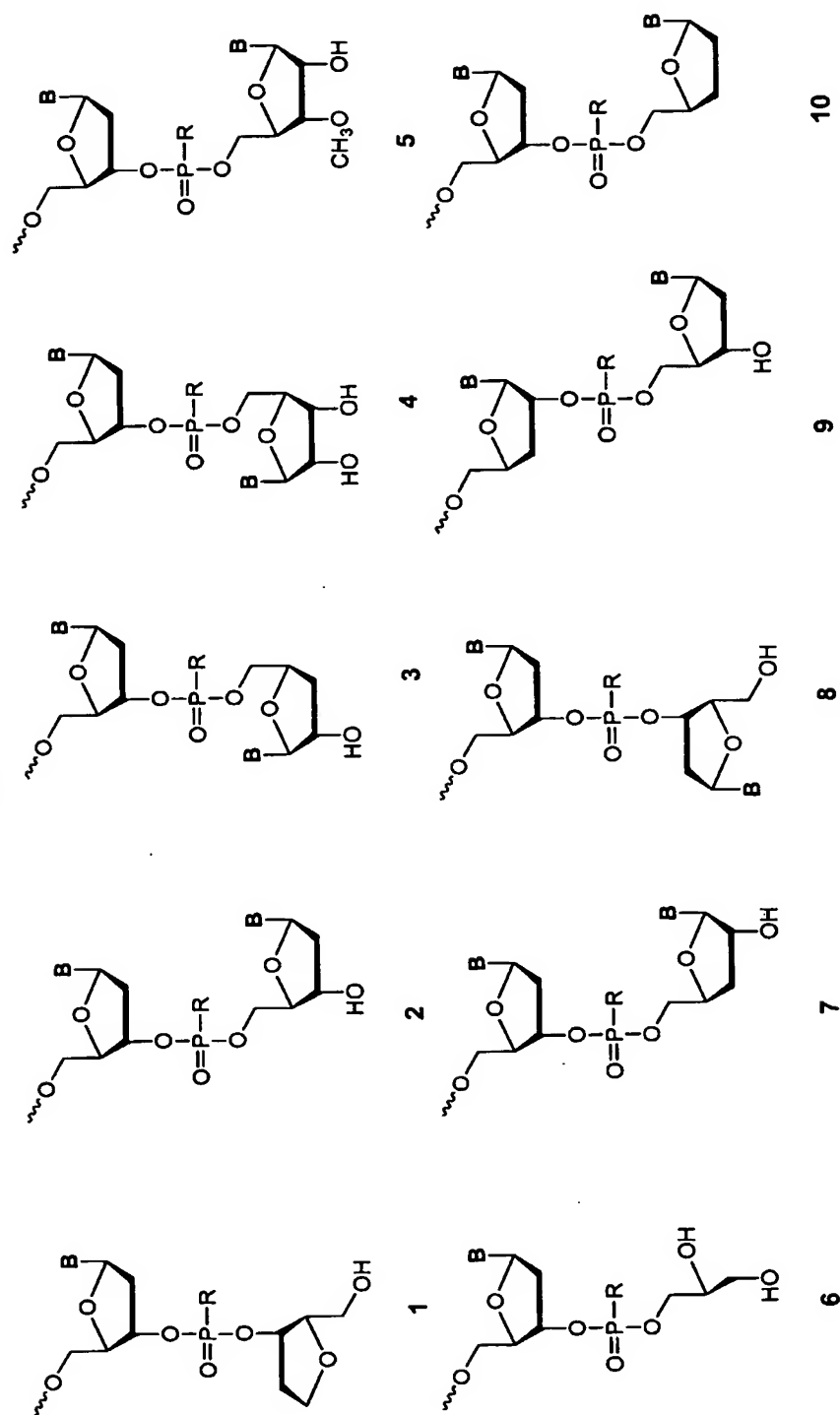




*Figure 9: Target site Selection using siRNA*





*Figure 10*

R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl  
 B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

**Figure 11: Modification Strategy**

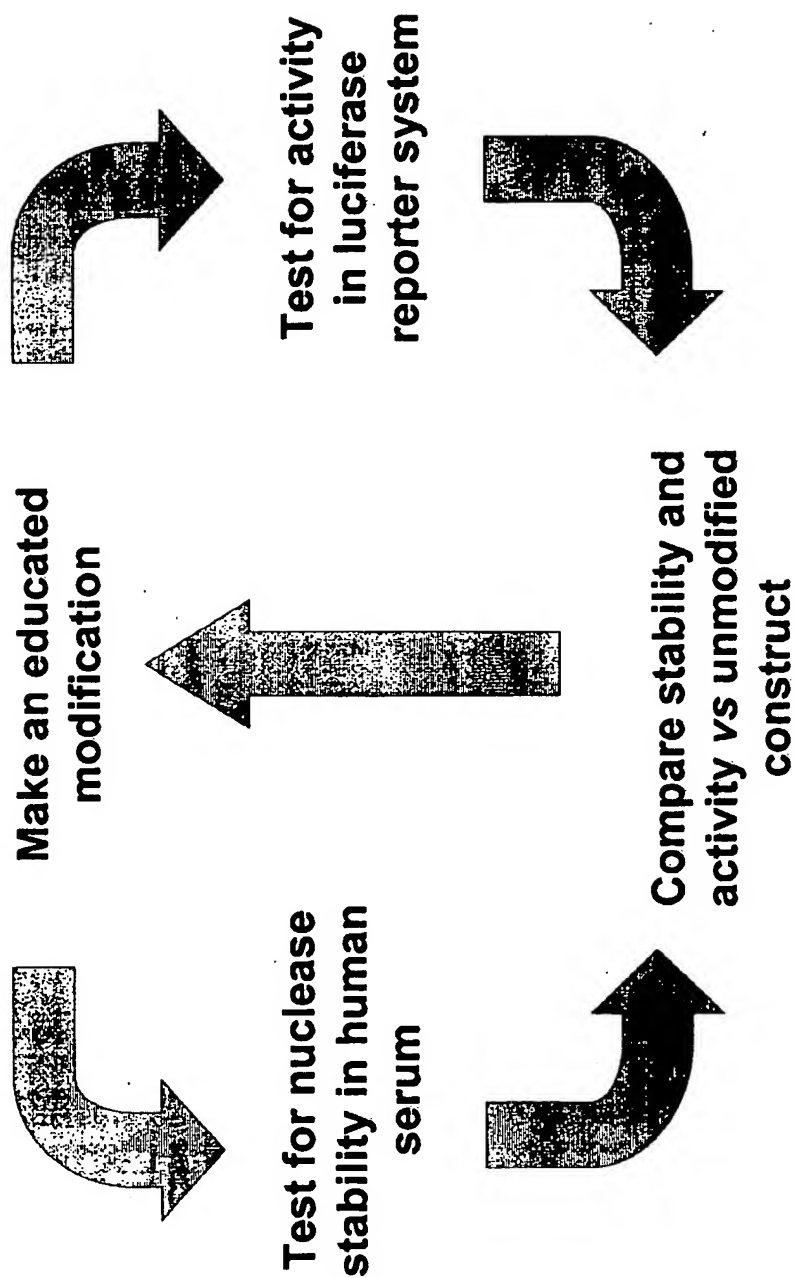
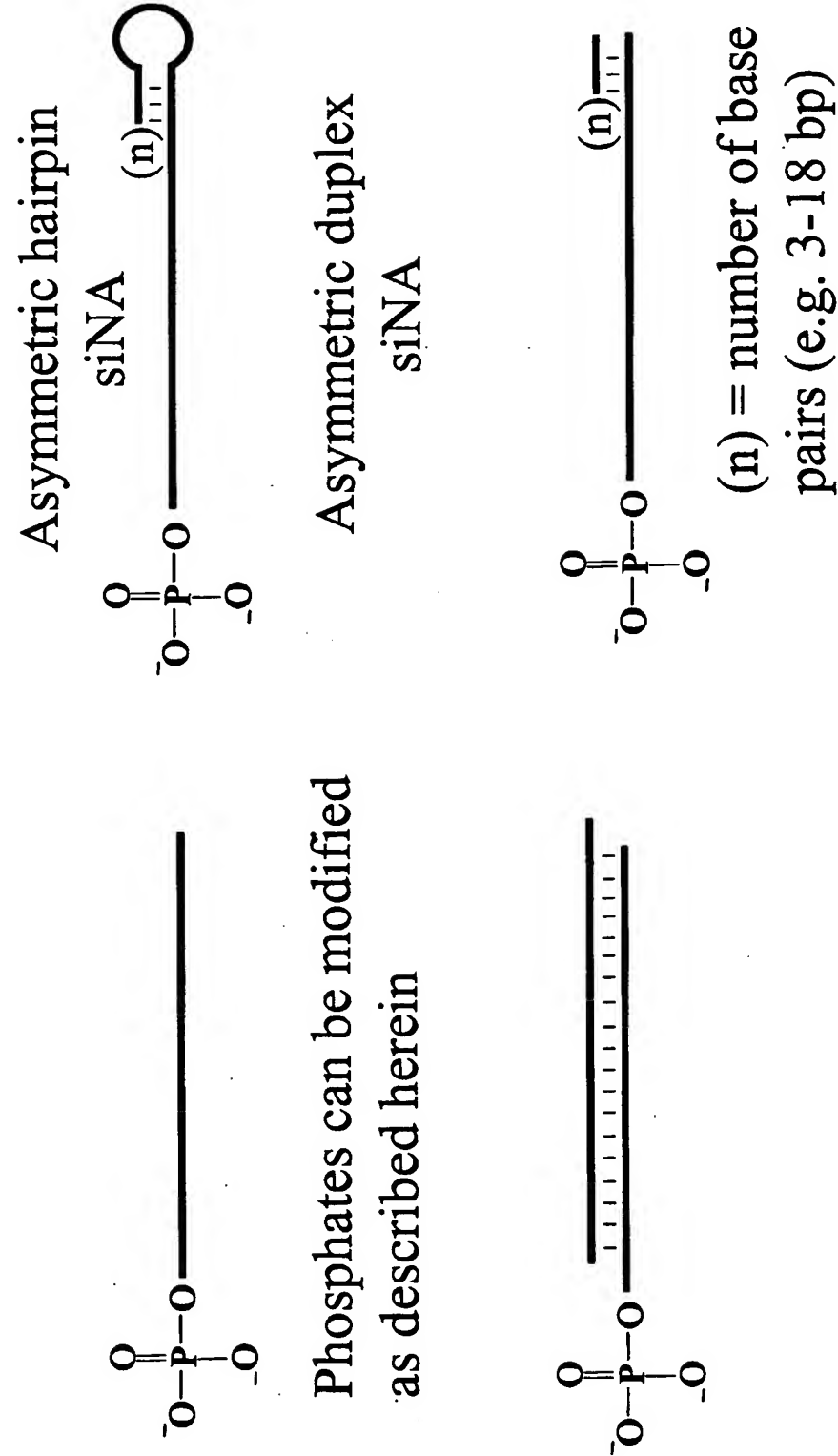
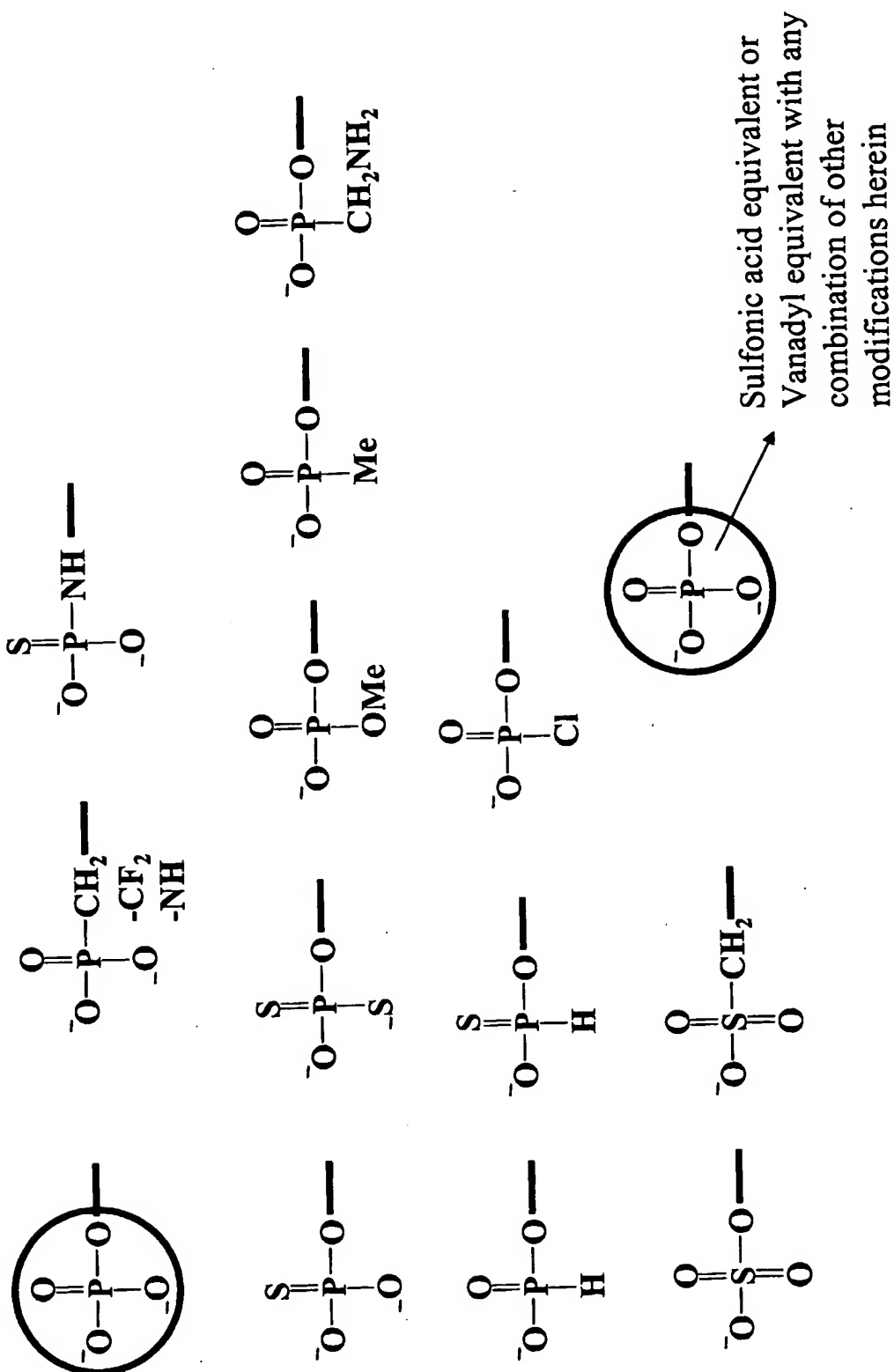


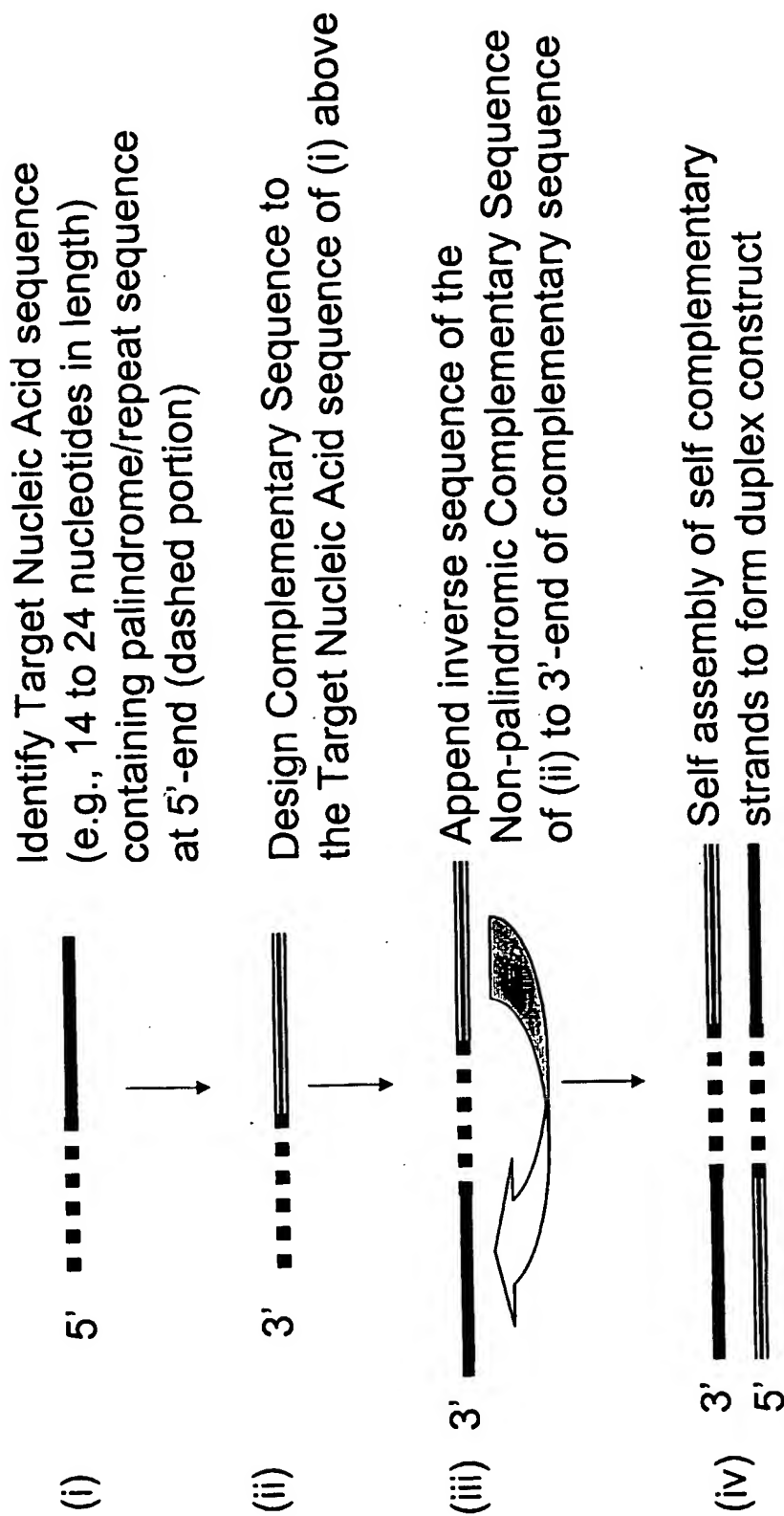
Figure 12: Phosphorylated siNA constructs



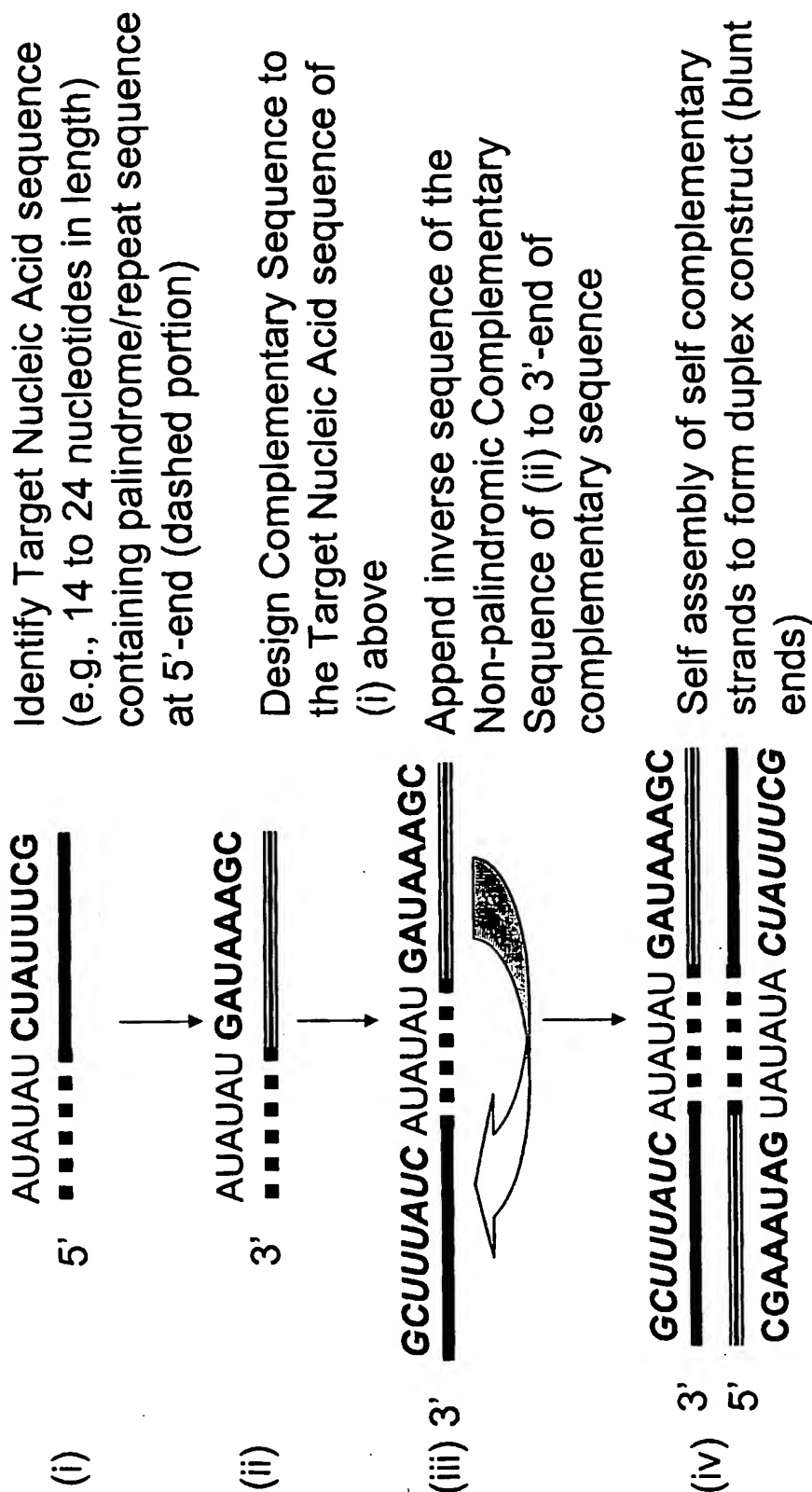
*Figure 13: 5'-phosphate modifications*



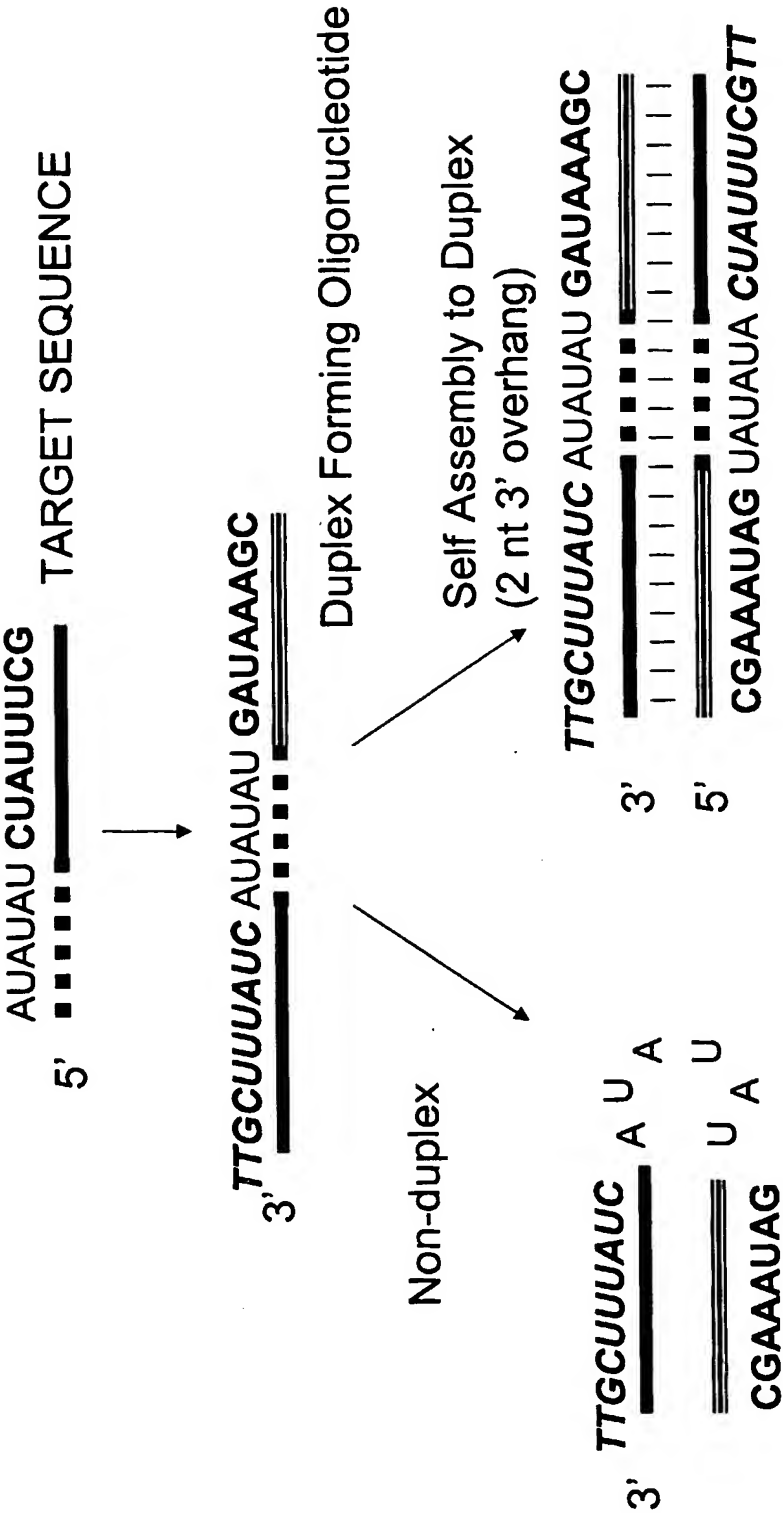
**Figure 14A: Duplex forming oligonucleotide constructs that utilize palindrome or repeat sequences**



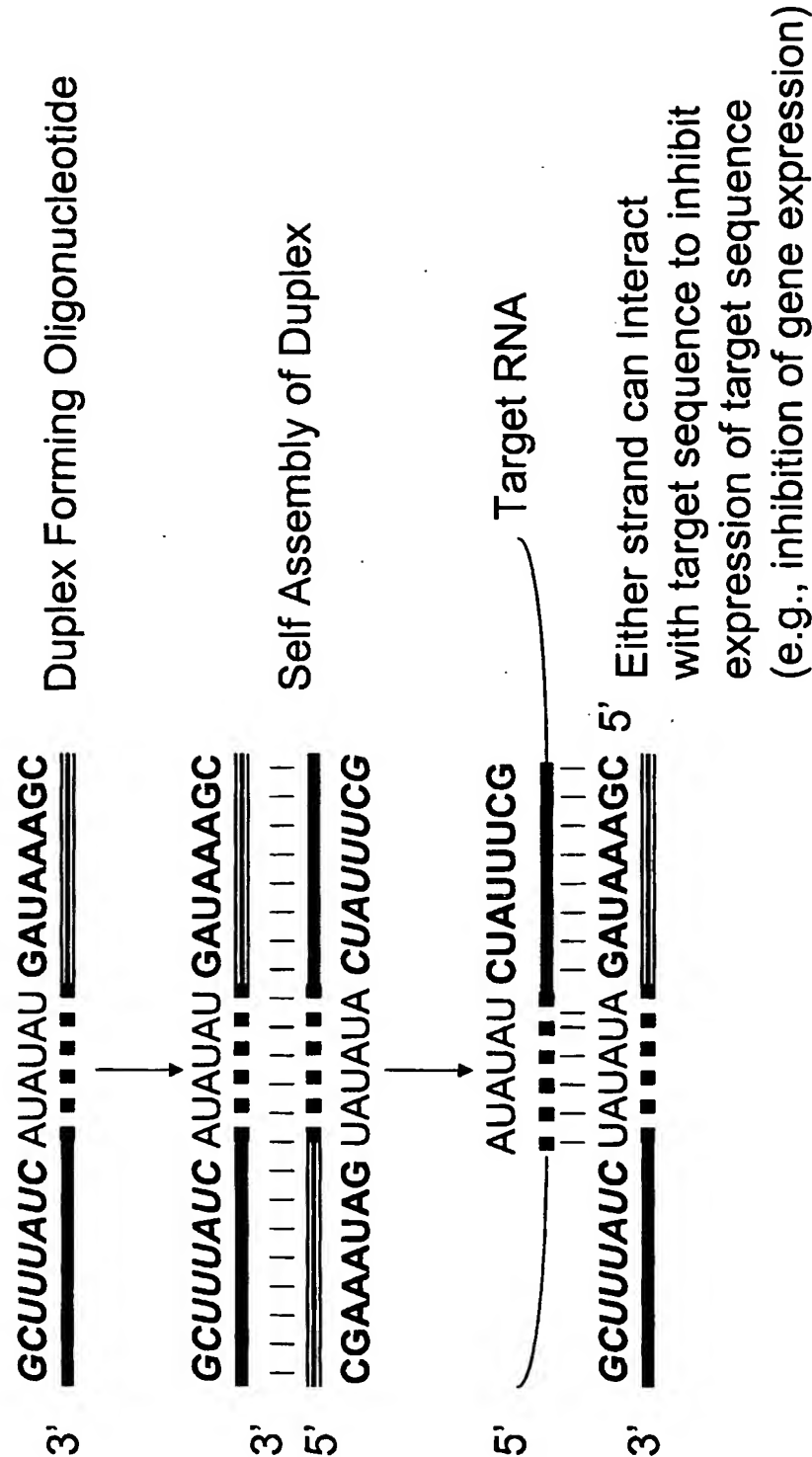
**Figure 14B: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence**



**Figure 14C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly**

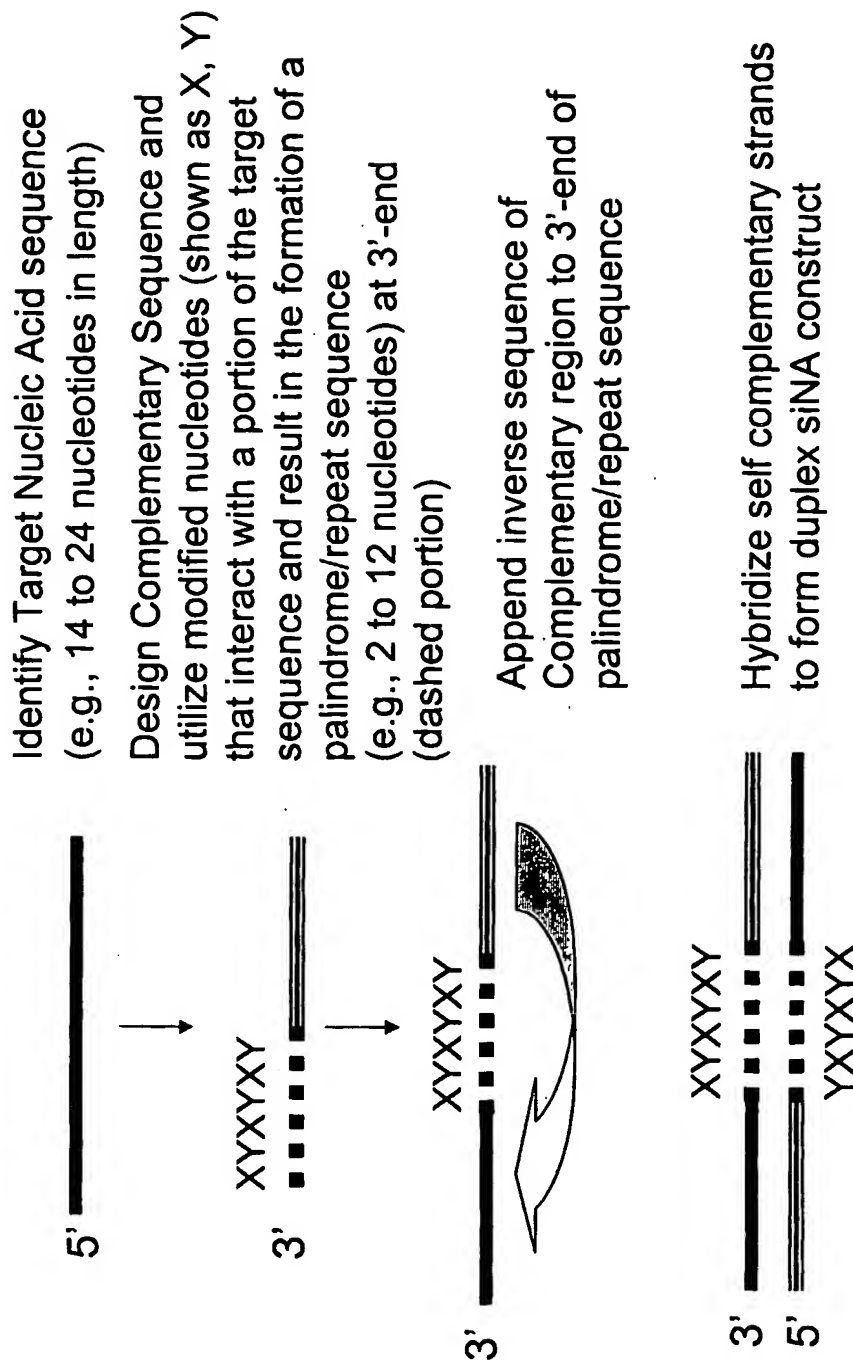


**Figure 14D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition of Target Sequence Expression**

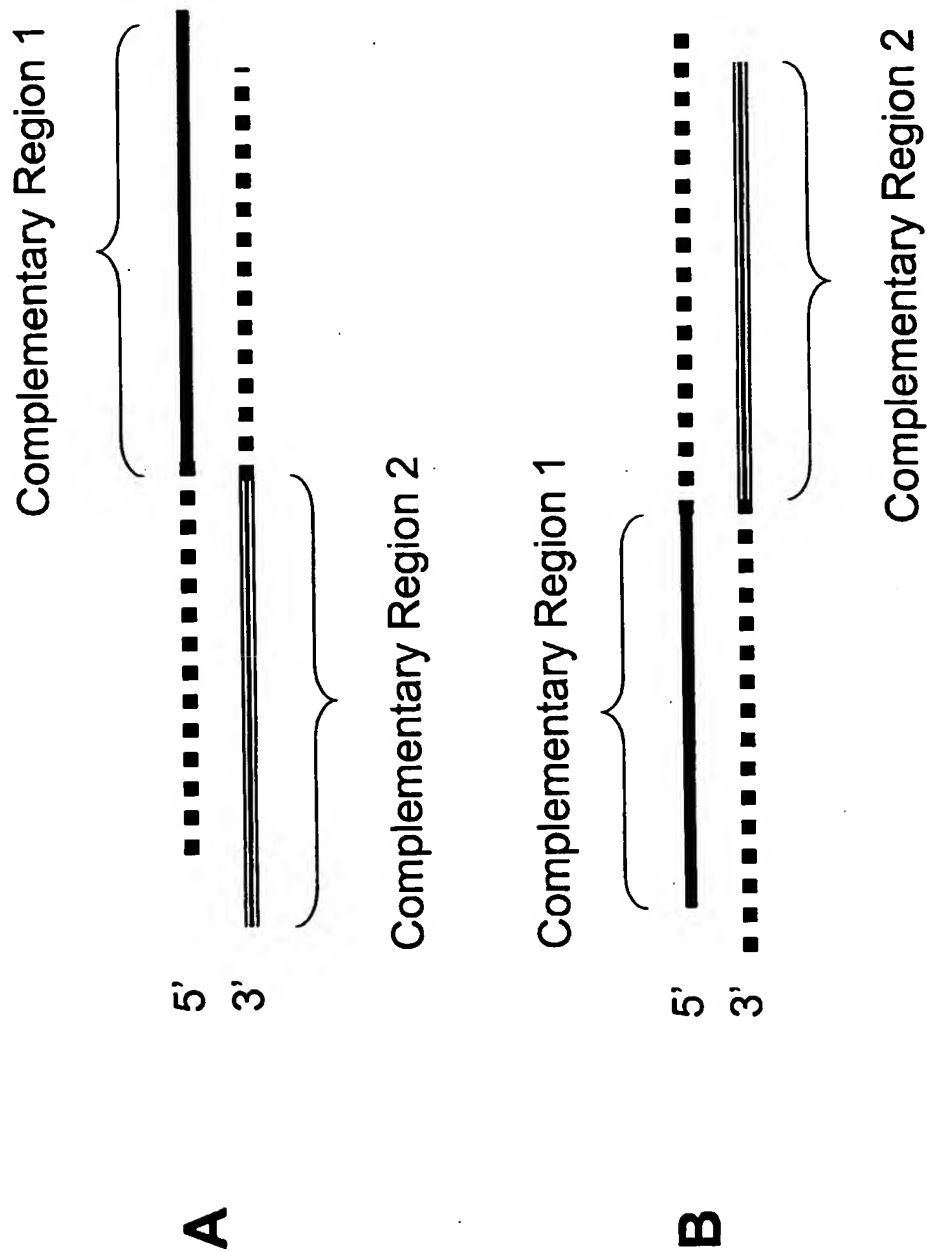




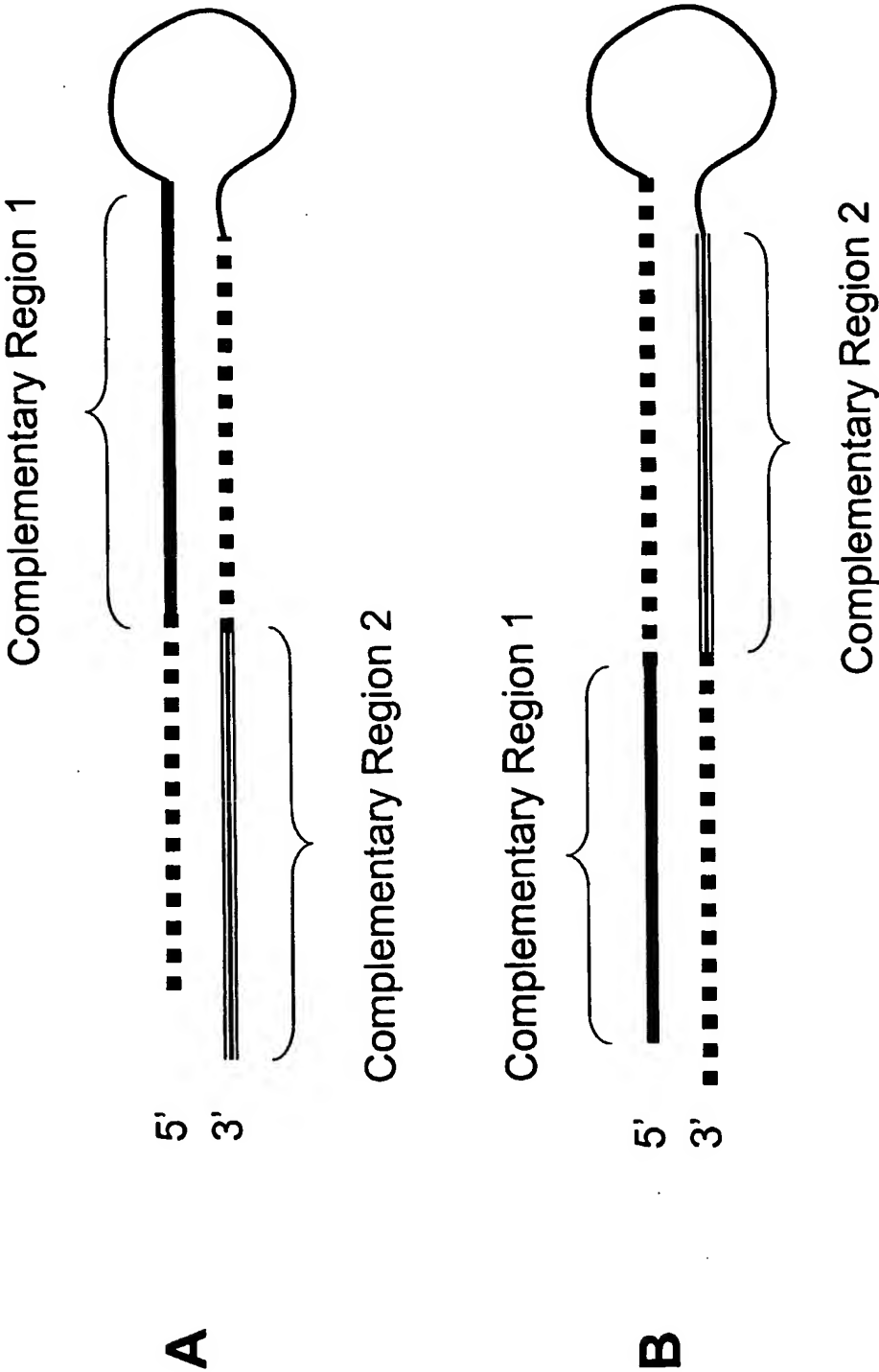
**Figure 15: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences**



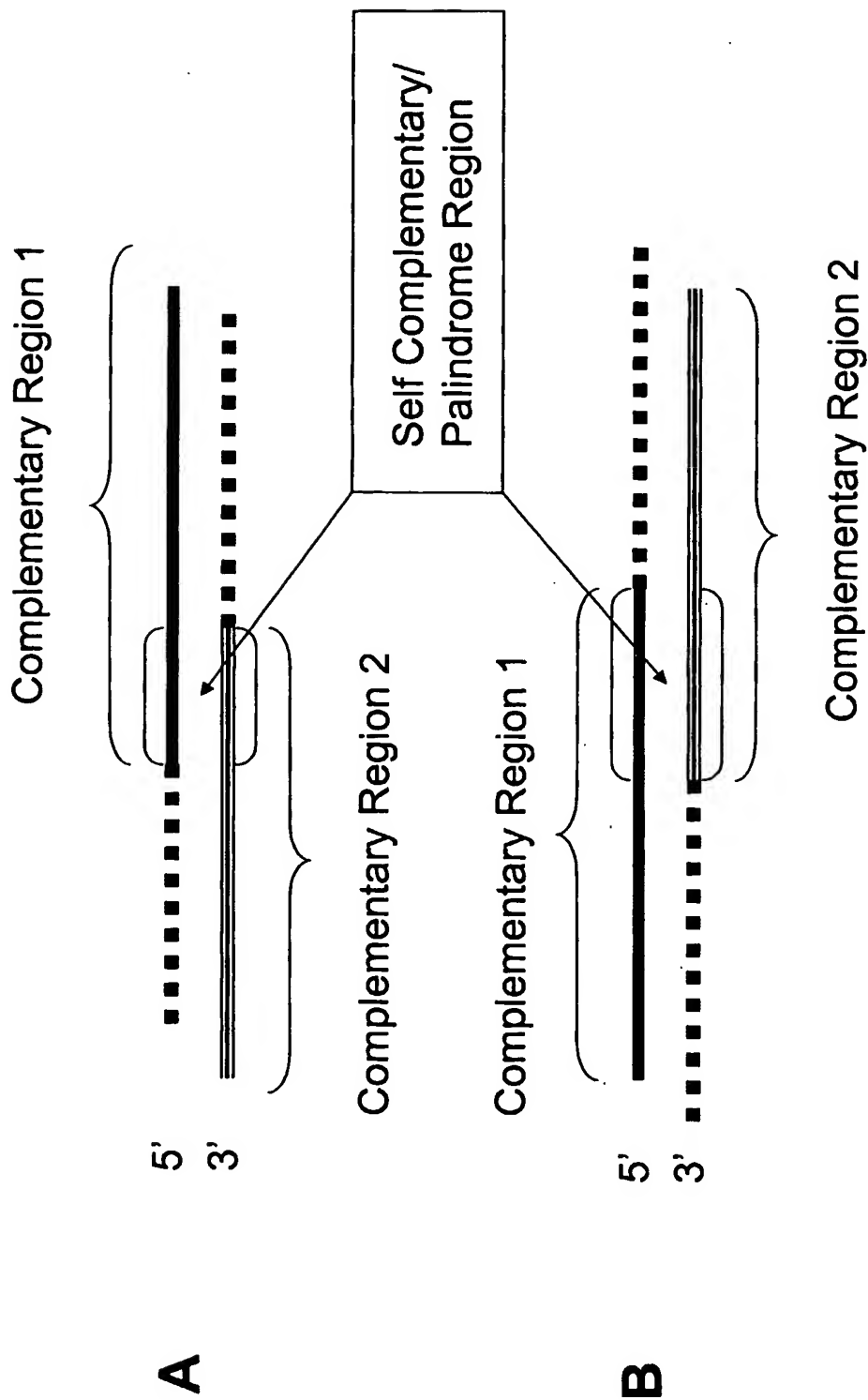
**Figure 16: Examples of double stranded multifunctional siNA constructs with distinct complementary regions**



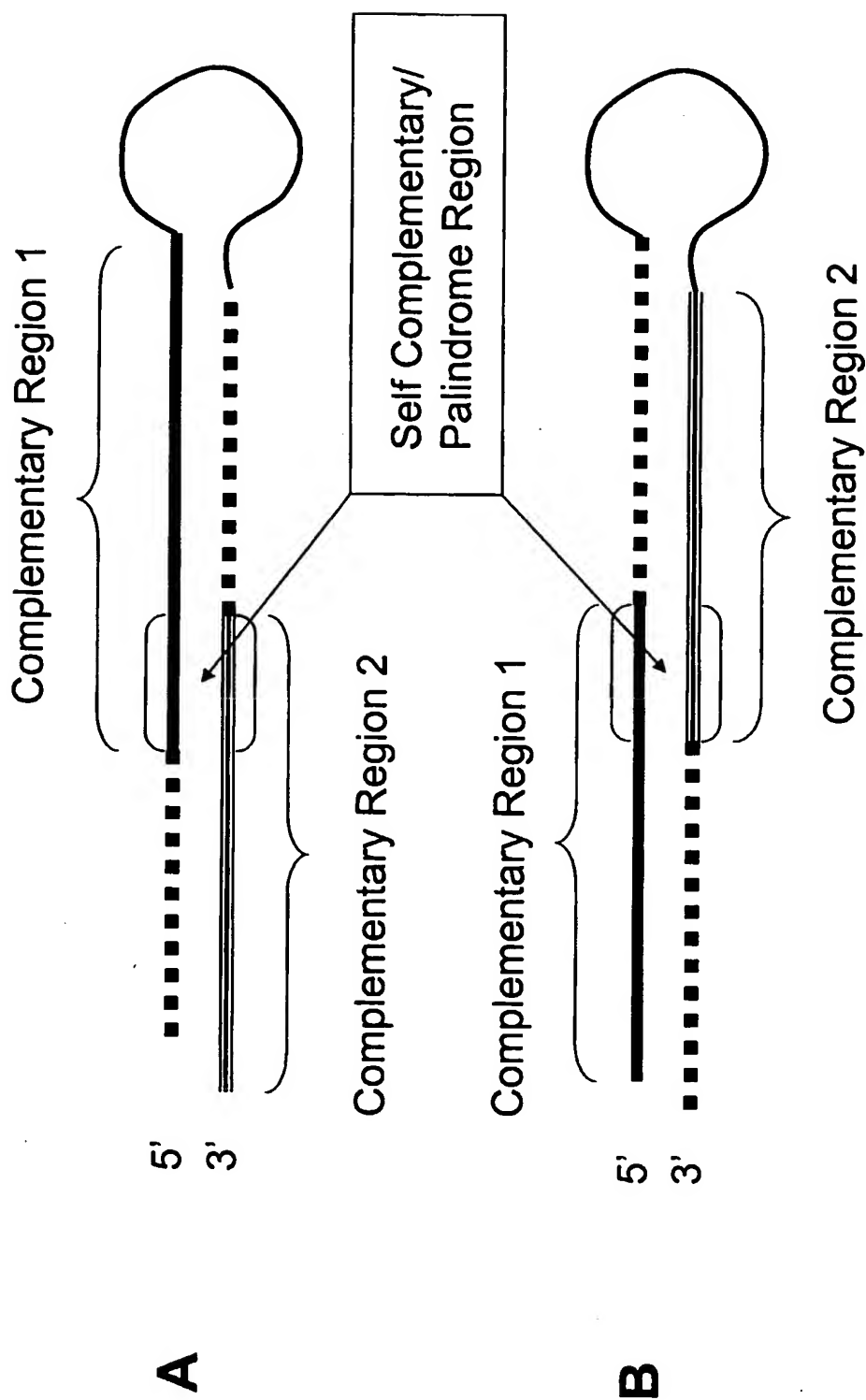
**Figure 17: Examples of hairpin multifunctional siNA constructs with distinct complementary regions**



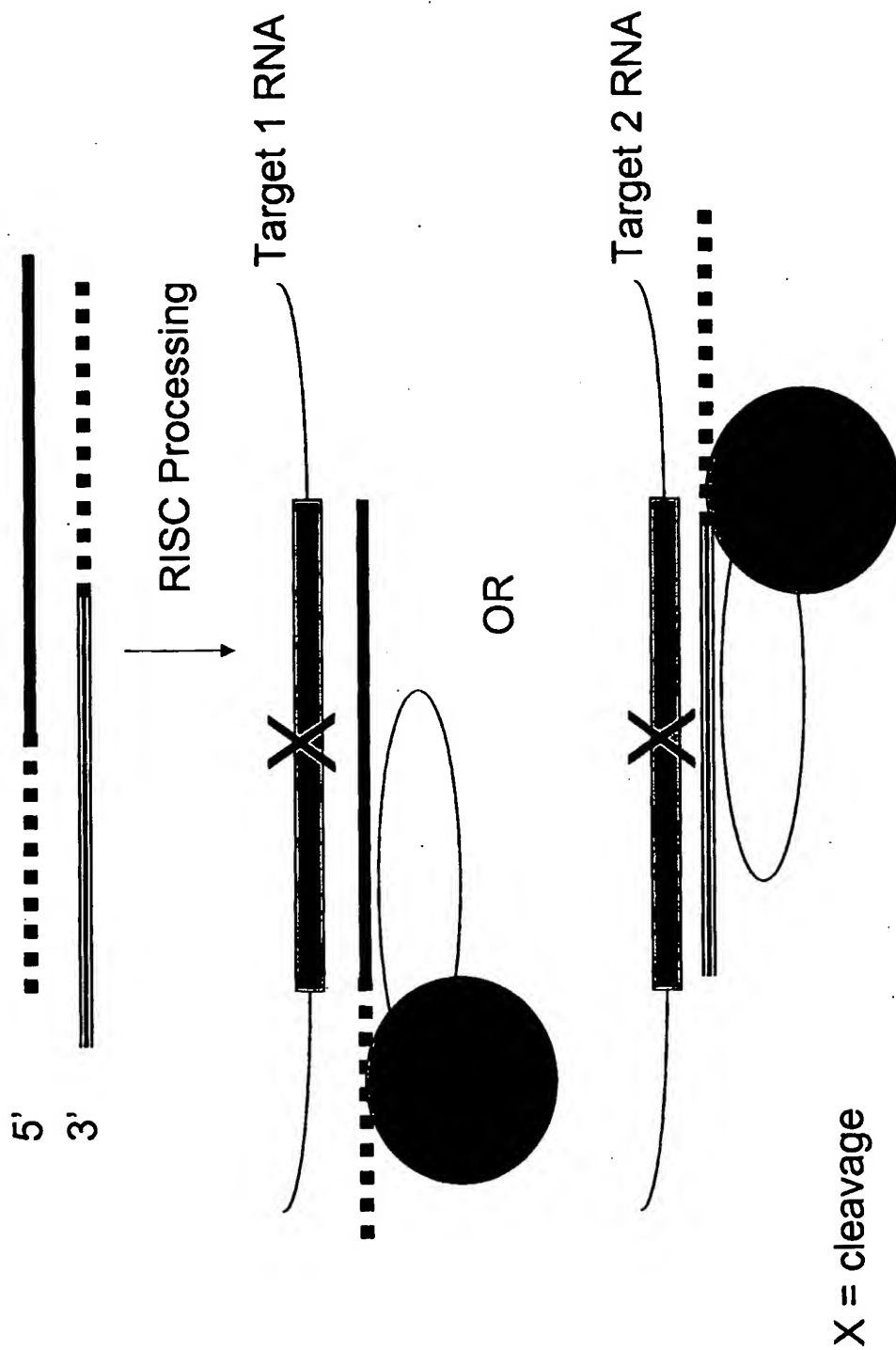
**Figure 18: Examples of double stranded multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region**



**Figure 19: Examples of hairpin multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region**



**Figure 20: Example of multifunctional siNA targeting two separate  
Target nucleic acid sequences**



**Figure 21: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence**

